Familial colorectal cancer 2.0

Implementation of guidelines on familial and hereditary colorectal cancer

Nicky Dekker

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Implementation of guidelines on familial and hereditary colorectal cancer

Proefschrift

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volgens besluit van het college van decanen
in het openbaar te verdedigen op dinsdag 23 april 2013
om 13:30 uur precies

door

Nicky Dekker
geboren op 25 juni 1984
te Amsterdam

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Stellingen behorende bij het proefschrift

"Familial colorectal cancer 2.0: Implementation of guidelines on familial and hereditary colorectal cancer"

1. Mensen met een verhoogd familiair risico op colorectaal carcinoom die daarom verwezen zouden moeten worden voor preventieve maatregelen, worden dat vaak niet (2 op 3). *(dit proefschrift)*

2. Om betere verwijzingen voor preventieve maatregelen vanwege een verhoogd familiair risico op colorectaal carcinoom te realiseren, is het nodig om de kennis van artsen en het bewustzijn van patiënten en hun familieleden te verbeteren. *(dit proefschrift)*

3. Het afnemen van de familieanamnese en het op indicatie aanvragen van onderzoek naar microsatellietinstabiliteit in tumorweefsel gebeurt bij de meeste patiënten met colorectaal carcinoom. Het verzamelen van deze gegevens leidt echter onvoldoende tot verwijzing voor preventieve maatregelen wanneer deze maatregelen geïndiceerd zijn. *(dit proefschrift)*

4. Patiënten willen vooral advies van hun arts wanneer het gaat om het nemen van preventieve maatregelen vanwege een verhoogd familiair risico op colorectaal carcinoom. *(dit proefschrift)*

5. Digitale en papieren hulpmiddelen hebben een positief effect op belangrijke uitkomstmaten als communicatie en kennis van patiënten met colorectaal carcinoom. *(dit proefschrift)*

6. Een goed elektronisch patiëntendossier kan het medisch dossieronderzoek aanzienlijk bespoedigen. *(Wang, PLoS ONE 2012)*

7. If you can dream it, you can do it. *(Walt Disney)*

8. De tijd hebben is de tijd nemen.

9. Don't compromise yourself, you're all you've got. *(Janis Joplin)*

10. Er is geen weg naar geluk; het geluk is de weg. *(Boeddha)*

Nicky Dekker
23 april 2013

Uitnodiging

Voor het bijwonen van de
openbare verdediging van
mijn proefschrift

Familial colorectal cancer 2.0
Implementation of guidelines on familial and hereditary colorectal cancer

Op 23 april 2013 om 13:30 uur
in de Aula van de
Radboud Universiteit,
Comeniuslaan 2 te Nijmegen

U bent van harte welkom bij de
plechtigheid en de aansluitende
receptie bij Restaurant Valdin,
Van Peltlaan 4 te Nijmegen

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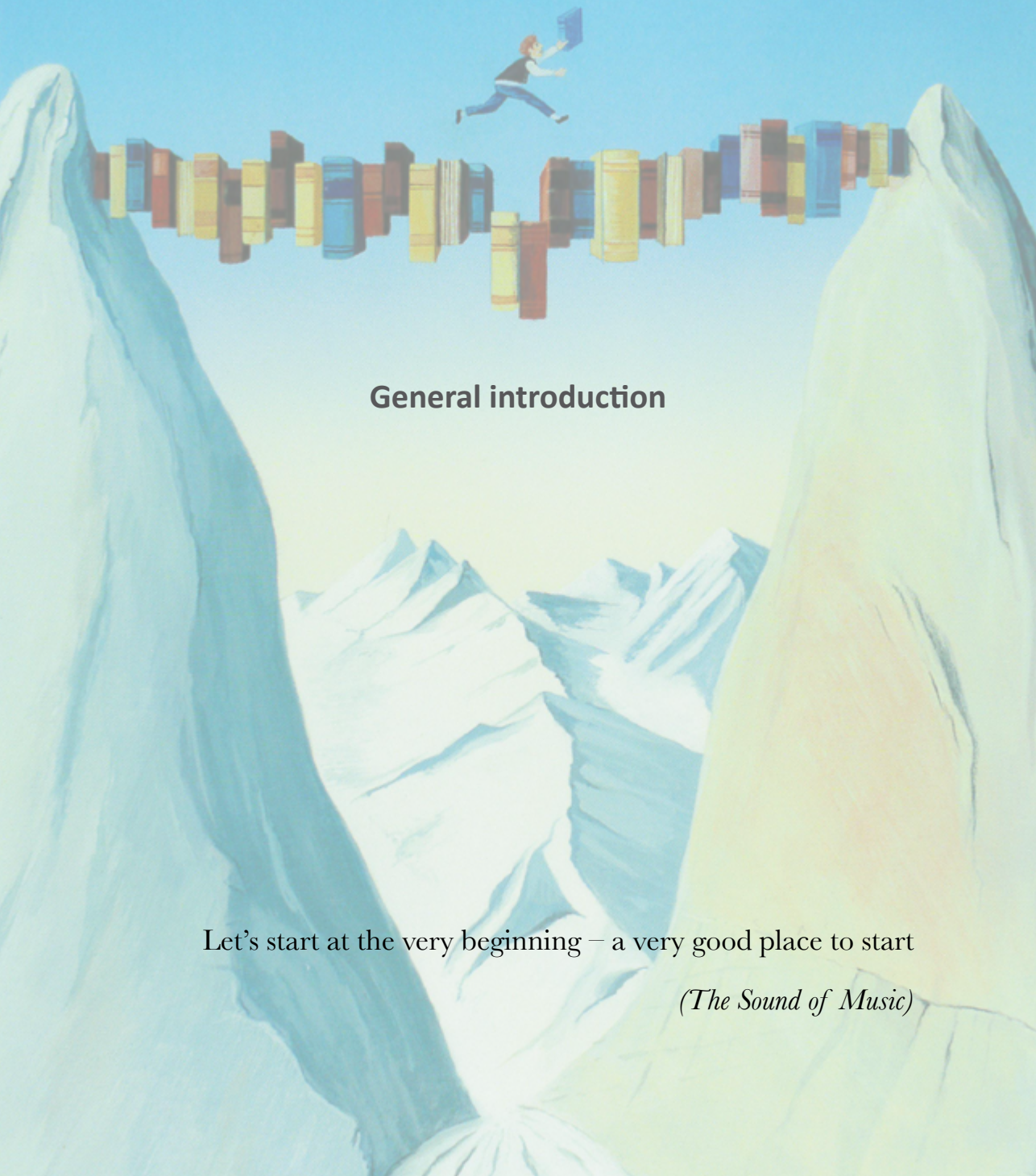
CONTENT

Chapter 1



General introduction

Let's start at the very beginning – a very good place to start

(The Sound of Music)

INTRODUCTION

For individuals with an increased familial colorectal cancer (CRC) risk, preventive measures such as surveillance colonoscopies have been shown to be highly effective in decreasing their cancer risk with up to 80%.[1,2] For effective use of these preventive measures, at-risk individuals need to be identified as such, followed by adequate referral, while those without such familial risk can be reassured that no such preventive measures are needed. These recommendations form the basis for the Dutch multidisciplinary guideline on hereditary CRC, which was developed in 2008.[3]

However, previous studies have shown that implementation of similar guidelines proved to be difficult. As a result, only 12-30% of individuals with an increased familial CRC risk are referred for adequate preventive measures.[4-11] For more effective cancer prevention, this percentage needs to be increased. Therefore, this thesis focuses on studying 1) current care regarding the identification and referral of individuals with an increased familial CRC risk and 2) several strategies to improve guideline implementation, particularly regarding familial CRC risk assessment, interpretation (i.e. determination of appropriate preventive measures) and communication.

In this introductory chapter, the identification and referral of individuals with an increased familial colorectal cancer (CRC) risk are addressed. First, more detailed information about the familial CRC risk and corresponding preventive measures is provided. Next, different ways to identify those with an increased familial CRC risk are addressed, as well as the current situation regarding referral for preventive measures. After that, the rationale for a strategy aimed at improvement of familial CRC risk identification and referral for preventive measures is described, followed by the main goal of the study described in this thesis, and by an overview of the thesis chapters.

FAMILIAL COLORECTAL CANCER RISK AND PREVENTIVE MEASURES

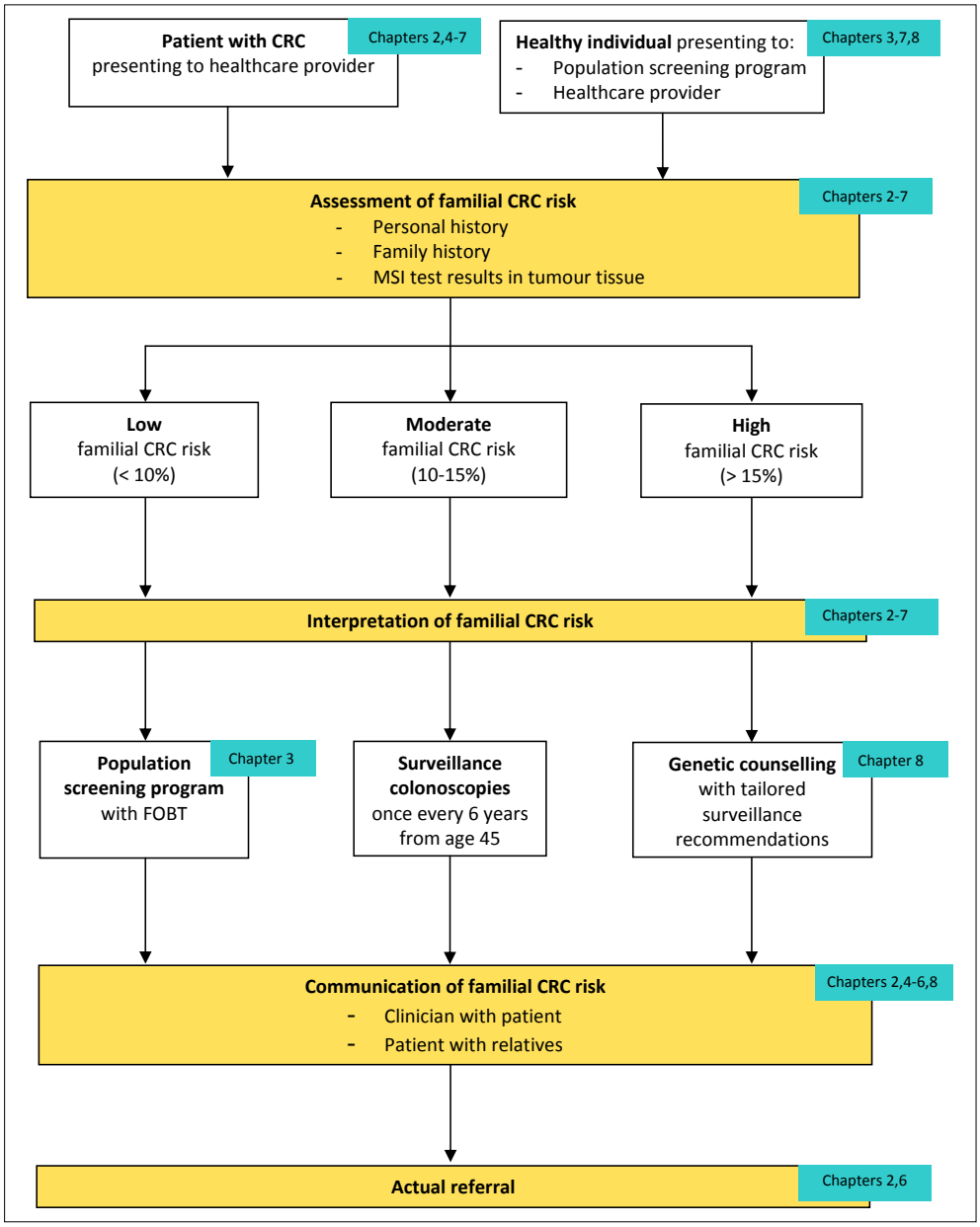
Identification of familial colorectal cancer risk

The familial CRC risk depends on the number of affected relatives, age at diagnosis, the presence of synchronous or metachronous adenomas, CRCs and other related tumours, and molecular characteristics of the tumours such as microsatellite instability (MSI).[12] Familial CRC risk is generally divided into three risk categories: high (cumulative familial CRC risk above 15%), moderate (10-15%), and low (below 10%).[3,13-15]

In essence, familial CRC risk assessment is similar for CRC patients and unaffected relatives. However, the setting in which familial CRC risk assessment, leading to the identification of families with an increased risk of CRC, is different for affected and unaffected individuals. As shown in figure 1, familial CRC risk assessment generally takes place in any of these three settings: 1) through a CRC patient presenting to a hospital clinician or other healthcare provider; 2) through an individual participating in the population screening program, where family history is assessed after a positive FOBT has been found; and 3) through a healthy person with a positive family history of cancer presenting to a general practitioner or other healthcare provider with questions about his/her familial CRC risk and need for surveillance. For practical reasons, this thesis focuses on the first two settings. The third is only addressed in the general discussion.

Since familial CRC risk identification can take place at various stages in the referral process (e.g. upon diagnosis by a gastroenterologist or surgeon, or after genetic counselling and testing), the final classification of familial CRC risk can change during this time. For example, a patient with CRC below the age of 50 and a negative family history is assumed to have a high familial CRC risk until MSI analysis has been performed, in which case the familial CRC risk is confirmed to be high (in case of an MSI-positive result) or changed to moderate (in case of an MSI-negative tumour).[15] Also, a more detailed family history taken by a clinical geneticist can lead to a higher or lower familial CRC risk than previously thought, because relevant tumours may prove to be of a different type when confirmed from pathology records, or age at diagnosis may differ. It is therefore important that clinicians use all available and relevant methods to identify increased familial CRC risk (e.g. perform MSI analysis if indicated).

Figure 1. Pathway for familial colorectal cancer identification and referral

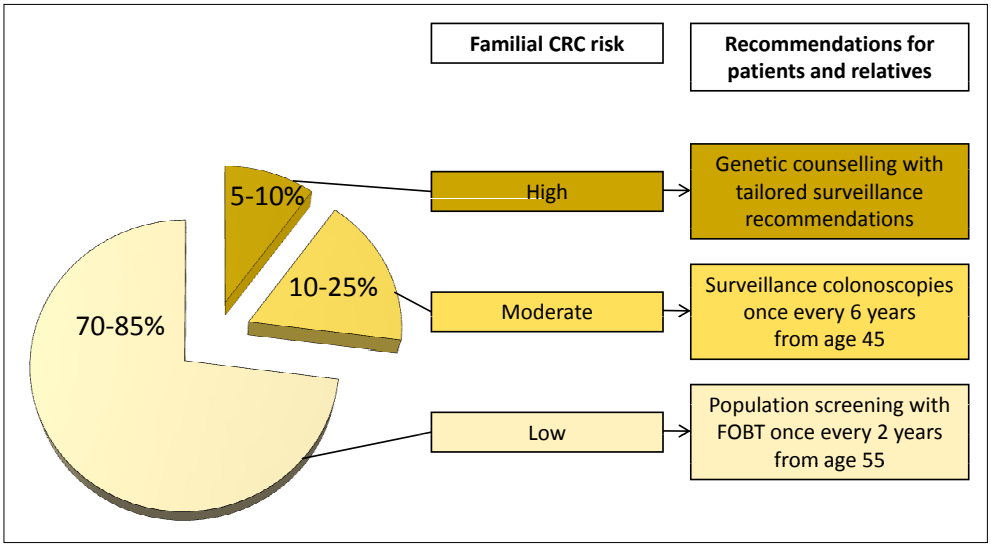


In figure 1, the pathway for familial colorectal cancer identification and referral is shown for colorectal cancer patients and individuals unaffected with cancer. Recommendations for preventive measures are in accordance with national guidelines.[3] Chapters of this thesis in which the items are addressed are shown.
CRC: colorectal cancer; FOBT: faecal occult blood test; MSI: microsatellite instability analysis

Preventive measures

For each familial CRC risk category, different preventive measures are recommended to decrease CRC risk, such as colonoscopies in case of an increased familial CRC risk, and faecal occult blood tests in case of a low familial CRC risk.[3,13-16] Individuals with a high familial CRC risk are recommended to attend genetic counselling, where tailored surveillance advice is given.[3] Besides the type, the frequency and starting age of these measures vary per familial CRC risk category, as shown in figures 1 and 2. Details of these risk categories and preventive measures are described in the following paragraphs.

Figure 2. Recommended preventive measures by familial colorectal cancer risk category



In figure 2, the familial colorectal cancer risk levels (i.e. the cumulative lifetime risk of developing colorectal cancer for patients' first-degree relatives) are shown with the corresponding recommendations for preventive measures in accordance with national guidelines.[3]
CRC: colorectal cancer

High familial CRC risk

Definition

Approximately 5-10% of CRC patients have a high familial CRC risk, meaning that their relatives have a cumulative lifetime risk of developing CRC of more than 15%.[17,18] Moreover, these patients have an increased risk of developing metachronous CRCs themselves, which may be as high as 29% within ten years.[19-21] Genetic causes play a major role in the development of CRCs in these high-risk families.

Genetic counselling and testing

In international and national guidelines, genetic counselling is recommended for individuals with a high familial CRC risk.[3,14,15] Based on a more detailed pedigree analysis and DNA analysis, a clinical geneticist can then diagnose the presence of a hereditary CRC syndrome such as Lynch syndrome. Among other things, cancer risks, tailored surveillance recommendations and consequences for the patient and their relatives are communicated at the familial cancer clinic. Relatives who test negative for a mutation that runs in the family can be reassured that their cancer risk is not increased.[22] In table 1, the Dutch guideline referral criteria for genetic counselling are shown, which are based on age at diagnosis, personal and family history of adenomas, CRC and/or other Lynch syndrome associated tumours, and molecular characteristics such as microsatellite instability (MSI).

Lynch syndrome

The most common hereditary CRC syndrome is Lynch syndrome, previously known as Hereditary Nonpolyposis Colorectal Cancer (HNPCC). This autosomal dominant syndrome is caused by mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS2* and the more recently discovered *EPCAM* gene.[23] Other hereditary CRC syndromes, such as Familial Adenomatous Polyposis syndrome (FAP), are even more rare than Lynch syndrome and have a distinct clinical phenotype with many adenomas; therefore, these syndromes fall outside the scope of this thesis.

Cancer risk

Lynch syndrome mutation carriers have high risks of CRC (12-83%), endometrial cancer (15-80%), and increased risks of other Lynch syndrome associated tumours, including ovarian, gastric and urothelial cancer.[24-36] Mean age at diagnosis of these cancers in Lynch syndrome is significantly lower than in the general population: 41-54 years for CRC (versus 70 years in the general population) and 54-59 years for endometrial cancer (versus 68 years in the general population).[32-35]

Preventive measures

To decrease the risk of developing (metachronous) cancers, surveillance recommendations for Lynch syndrome mutation carriers include surveillance colonoscopies every 1-2 years from age 25, annual gynaecological surveillance from age 30-35, and in selected families, surveillance for urothelial and gastric cancer as well.[3,21,37-39] Performing surveillance colonoscopies in Lynch syndrome mutation carriers has been proven to decrease CRC-related morbidity and mortality with up to 65%.[1]

Treatment

Besides affecting cancer prevention in patients and relatives, familial risk identification and genetic testing also influence treatment decisions. For example, patients with Lynch syndrome may benefit from subtotal colectomy instead of limited resection to decrease their risk of metachronous CRCs.[19-21] Furthermore, patients with Lynch syndrome associated CRCs seem not to benefit from 5-FU-based chemotherapy.[40]

Table 1. Referral criteria for genetic counselling

Dutch guideline referral criteria for genetic counselling for hereditary colorectal cancer

Healthy individual, or patient with MSI-negative colorectal cancer, and:
- First-degree relative with colorectal or endometrial cancer before age 50
- Three or more (first- or second-degree) relatives with colorectal cancer or a Lynch syndrome associated tumour before age 70
- Mismatch repair gene mutation in the family

Patient with colorectal cancer and:
- Age at diagnosis before age 50
- First-degree relative with colorectal cancer or a Lynch syndrome associated tumour before age 50
- Second colorectal cancer before age 70
- Colorectal cancer and a Lynch syndrome associated tumour before age 70
- Two or more (first- or second-degree) relatives with colorectal cancer or a Lynch syndrome associated tumour before age 70
- MSI-positive colorectal cancer

Patient with colorectal adenoma with high-grade dysplasia before age 40
Patient with a Lynch syndrome associated tumour before age 50

Individual with a personal history or first-degree relatives with:
- Adenomatous polyposis
- Pathogenic mutation in the APC gene
- Biallelic pathogenic mutations in the MUTYH gene
- More than ten synchronous or metachronous colorectal adenomas before age 60 *

In table 1, referral criteria for genetic counselling for hereditary colorectal cancer are shown.[3] Individuals who meet one or more of these criteria have a high familial colorectal cancer risk and are recommended to attend genetic counselling to receive tailored surveillance recommendations.
* As the likelihood of a genetic abnormality increases if the person is younger and/or the number of adenomas is greater, referral for genetic counselling should also be considered for young patients with less than 10 colorectal adenomas and for patients ≥ 60 years old with many adenomas.

APC: adenomatous polyposis coli; First-degree relatives: parents, siblings and children; Lynch syndrome associated tumours: malignancies of the endometrium, stomach, small intestine, bile ducts, ovaries, upper urinary tract and adenoma or carcinoma of the sebaceous glands; MSI: microsatellite instability; MUTYH: mutY homolog; Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren.

Moderate familial CRC risk

Definition

In 10-25% of CRC patients, familial clustering of CRC and/or a young age at diagnosis is seen, but without molecular evidence of genetic syndromes such as Lynch syndrome.[17,18,41,42] In these families, the familial CRC risk is moderately increased (cumulative lifetime risk of 10-15%).[37,43,44]

Preventive measures

It is important to distinguish individuals with a high familial CRC risk from moderate-risk individuals, as in the latter group, less stringent preventive measures are recommended than in the high-risk group. Performing surveillance colonoscopies every 6 years from age 45 has been shown to be cost-effective in these moderate-risk families.[45] In table 2, the referral criteria for surveillance colonoscopies for a moderate familial CRC risk from the Dutch guideline are shown.[3] Dove-Edwin et al compared moderate-risk individuals undergoing regular surveillance colonoscopies with a slightly higher frequency than in the Dutch guideline (mean time between colonoscopies: 4.6-5.1 years) to those who did not undergo surveillance, and showed that the incidence of CRC was 80% lower in the group undergoing colonoscopies.[2]

Table 2. Referral criteria for surveillance colonoscopies

Dutch guideline referral criteria for surveillance colonoscopies every 6 years from age 45
• Exclusion of hereditary colorectal cancer and diagnosis of familial colorectal cancer by a clinical geneticist
• Two first-degree relatives with colorectal cancer between age 50-70
• A first-degree relative with colorectal cancer between age 50-70 and a second-degree relative with colorectal cancer before age 70
• A first-degree relative with an MSI-negative colorectal cancer before age 50

In table 2, referral criteria for surveillance colonoscopies are shown.[3] Individuals who meet one or more of these criteria have a moderate familial colorectal cancer risk and are recommended to undergo surveillance colonoscopies once every 6 years starting at age 45.

First-degree relatives: parents, siblings and children; MSI: microsatellite instability; Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren.

Low familial CRC risk

Definition

Approximately 70-85% of all CRC cases are sporadic, meaning that these cases do not meet criteria for an increased familial CRC risk, and that environmental factors play an important role in their aetiology.[17,18] Cumulative lifetime risks of CRC for these individuals are equal to the population risk or slightly increased, but do not exceed 10%.[17]

Preventive measures

For individuals with a low familial CRC risk, participation in population screening programs is recommended.[16] In the Netherlands, this screening program will start in 2013 for individuals aged 55-75. The screening program includes biennial immunochemical faecal occult blood testing (FOBT), followed by colonoscopy in case of a positive FOBT result. Based on calculations from pilot studies, this program will prevent approximately 1400 deaths due to CRC annually.[16] For effective cancer prevention, it is important to distinguish individuals with a low familial CRC risk eligible for population screening from those with an increased familial CRC risk, since earlier and more intensive surveillance with colonoscopies is indicated for the latter group.[3,16] The population screening program may serve as a good complementary method to identify individuals with an increased familial CRC risk and is therefore studied in this thesis.

IDENTIFICATION OF FAMILIAL COLORECTAL CANCER RISK

Multiple complementary data can be used to determine whether familial CRC risk is increased and preventive measures are indicated (figure 1): age at diagnosis, presence of synchronous or metachronous tumours, family history, and analysis of microsatellite instability (MSI) in tumour tissue.[12,46,47] Age at diagnosis is substantially lower in individuals with hereditary CRC syndromes (41-54 years versus 70 years in the general population) and thus can provide an important clue to the presence of such syndromes, as can the presence of multiple CRCs and other Lynch syndrome associated tumours in one patient or in a family.[32-35] Current Dutch guidelines recommend that clinicians take a family history for first- and second-degree relatives, including type of cancer and age of diagnosis.[3] Next, it is necessary to determine whether the patient is eligible for genetic counselling for a high familial CRC risk, surveillance colonoscopies without genetic counselling for a moderate familial CRC risk, or population screening with FOBT in case of a low familial CRC risk.[3,16] However, difficulties can be expected in each of these steps, thus limiting guideline implementation.

An important problem is that clinical criteria such as family history have been shown to miss up to 88% of Lynch syndrome mutation carriers, either because family history assessment was incomplete or because families do not meet the criteria but still carry a mismatch repair mutation.[12,47-50] Therefore, additional strategies are needed to identify individuals with an increased familial CRC risk. More than 95% of CRCs due to Lynch syndrome show MSI, in comparison to 15% of sporadic CRCs.[15] Current Dutch guidelines recommend performance of MSI analysis in all patients meeting the MIPA (MSI-testing-by-a-pathologist) criteria,

which include CRC before age 50 and a second CRC before age 70 (table 3).[3,45] However, MSI analysis is not always performed in patients meeting criteria for MSI analysis (e.g. age at diagnosis of CRC < 50 years), as shown by MSI analysis rates of 9-59% in previous studies.[5,51,52]

Table 3. Criteria for microsatellite instability analysis

Criteria for microsatellite instability analysis initiated by a pathologist (MIPA)
• Colorectal cancer before age 50 • Endometrial cancer before age 50 • Second colorectal cancer before age 70 • Colorectal cancer and other Lynch syndrome associated tumour before age 70

In table 3, the MIPA criteria (microsatellite instability analysis initiated by a pathologist) for newly diagnosed patients with colorectal cancer and other Lynch syndrome associated tumours are shown.[45] The Dutch guideline recommends that microsatellite instability analysis is performed by a pathologist in individuals who meet one or more of these criteria.[3]

Lynch syndrome associated tumours: malignancies of the endometrium, stomach, small intestine, bile ducts, ovaries, upper urinary tract and adenoma or carcinoma of the sebaceous glands

REFERRAL OF INDIVIDUALS WITH AN INCREASED FAMILIAL COLORECTAL CANCER RISK

After familial CRC risk identification, patients have to be referred adequately for preventive measures. Therefore, clinicians need to discuss the familial CRC risk and indicated preventive measures with their CRC patients, who in turn are asked to share this information with the relatives for whom it is relevant (figure 1).[3] Proper risk communication has been shown to improve adherence to surveillance recommendations and acceptance of genetic counselling by patients with an increased familial CRC risk, and to limit the use of these preventive measures by individuals without such risk.[53] However, familial CRC risk is only discussed by the clinician with a minority of patients (23% in a previous study).[4] This lack of risk communication is probably a major problem in the referral process of individuals with an increased familial CRC risk and provides an important target for improvement strategies.

The referral for patients after MSI analysis is a point of concern as well. Patients with an MSI-positive tumour need to be referred for genetic counselling, because such a test result is highly suggestive of a genetic predisposition for Lynch syndrome.[12,15] A study by Overbeek

et al has shown that only 59-77% of patients with MSI-positive tumours initiated by a pathologist are subsequently referred for genetic counselling.[51] In case of an MSI-negative tumour in patients meeting MIPA criteria in the absence of other high-risk criteria (such as other relatives meeting MIPA criteria or a clinical phenotype of polyposis), a moderate familial CRC risk is present.[15] In these moderate-risk families, patients and their first-degree relatives are recommended to undergo surveillance colonoscopies once every 6 years from age 45.[3] However, the percentage of patients and relatives who actually undergo surveillance colonoscopies is still unknown.

TARGETS FOR IMPROVEMENT

In spite of recommendations in international and national guidelines, the vast majority of CRC patients with an increased familial risk are not referred for preventive measures.[3-11] Recent Dutch studies have shown that only 15-30% of high-risk CRC patients visited a cancer genetics clinic.[4,5,8] In these studies, patients who were more likely to be referred included those in whom a complete family history was recorded, patients with whom referral was discussed, and patients who were treated in a teaching hospital. Studies from the UK, USA and Australia have shown comparable results.[6,7,9-11]

Several factors may contribute to these low referral rates. Previous studies have shown a general lack of awareness and knowledge of familial and hereditary CRC among clinicians as well as patients.[54-57] Family history is recorded in only 16-62% of CRC patients, while information necessary for familial risk assessment is often incomplete.[5,6,58] A large variation of 9-59% in MSI analysis rates exists in patients meeting criteria for MSI analysis.[5,51,52] Moreover, clinicians regularly interpret the results of family history and MSI analysis incorrectly, leading to under-referral of individuals with an increased familial CRC risk, and over-referral of individuals with a low or moderate familial risk.[7,51,59,60] Also, communication of the familial CRC risk between at-risk relatives is often incomplete.[61-64] Finally, not everyone wants to be referred for genetic counselling or surveillance colonoscopies if recommended. Uptake of surveillance colonoscopies in individuals with a moderate familial CRC risk ranged from 48-83% in previous studies, while uptake of genetic counselling among high-risk individuals ranged between 26-70%.[4,65-68]

It is not effective to focus on improving just one of these factors, if the rest of the referral process (figure 1) does not improve. In this thesis we examine each of these factors separately and evaluate the process as a whole, looking at familial CRC risk assessment,

interpretation and communication. We discuss several strategies and tools aimed at improving familial CRC risk identification, as well as referral of individuals with an increased familial CRC risk. The focus is on CRC patients, whereas less attention will be paid to relatives who may be at increased risk of developing CRC themselves. While these relatives often present themselves to general practitioners and other healthcare providers with questions about their familial CRC risk and eligibility for preventive measures, patients with CRC are the first one in the family to provide a clue to the possible presence of an increased familial CRC risk. These patients have therefore been selected as a starting point for the studies in this thesis. Additionally, the population CRC screening program is explored as a resource for further improving the identification of individuals with an increased familial CRC risk.

GUIDELINE DEVELOPMENT, IMPLEMENTATION AND EVALUATION

Guideline development

In general, guidelines are developed to support clinicians in their clinical decision making, improve outcomes for patients and ensure efficient use of healthcare resources, by providing recommendations which are based on the best available evidence.[69-71] In 2008, the multidisciplinary evidence-based guideline "Hereditary colorectal cancer" was developed in the Netherlands.[3] The guideline contains recommendations for referral of CRC patients and their relatives with an increased familial CRC risk for surveillance colonoscopies and genetic counselling. Referral criteria for preventive measures for the high and moderate familial CRC risk categories and for MSI analysis (tables 1-3) are clearly described in the guideline.[3,45]

Guideline implementation and evaluation

The Dutch hereditary CRC guideline was distributed among clinicians from relevant medical specialties by mail and made available online on http://www.oncoline.nl. However, implementation of guidelines by simple dissemination is known to be largely ineffective.[72-74] No single implementation strategy has been found to be effective by itself, and implementation strategies that are effective in one setting may prove futile in others.[72,75] Therefore, Grol et al proposed a framework for changing clinical practice, which includes the development of a concrete proposal for change; analysis of the target setting by measuring current care and to identify obstacles to change; linking interventions to needs, facilitators, and obstacles to change; development of an implementation plan; and monitoring progress with implementation.[72,76]

During the development of the hereditary CRC guideline, experts agreed that spontaneous guideline implementation would be unlikely, as familial CRC risk assessment, interpretation and communication, which are necessary for adequate risk identification and referral, are relatively new tasks to many clinicians outside the field of medical genetics. It also means that clinicians need to consider not only the patient in front of them, but have a responsibility towards their relatives as well. Clinicians and patients from the guideline development committee expected that the main implementation barriers would be clinicians' lack of knowledge and skills in familial CRC risk assessment, interpretation and communication, as well as a lack of awareness of the subject among CRC patients.

To increase implementation of the hereditary CRC guideline, a multi-faceted strategy called RISCO (risk of colorectal cancer) was developed, aimed at both CRC patients and clinicians. To improve clinicians' knowledge and skills of familial CRC risk assessment, referral for preventive measures and communication of the familial risk, the strategy for clinicians consisted of education, the RISCO website with information on familial CRC risk and preventive measures as well as risk calculators, and pocket cards with the guideline referral criteria.[3] To enhance patients' knowledge, familial CRC risk perception, and uptake of preventive measures, a brochure with information on familial CRC risk and preventive measures was developed, as well as a part of the RISCO website with similar information, risk calculators and a decision support intervention. After pilot tests among CRC patients and clinicians, the multi-faceted implementation strategy was evaluated in a clustered randomised controlled trial, both regarding effectiveness and feasibility (i.e. use of and experiences with the strategy). This evaluation forms the basis for this thesis. Additional studies were performed to evaluate possible manners in which to improve the identification of and care for individuals with an increased familial CRC risk. These include a study on the prevalence of an increased familial CRC risk among participants in the population CRC screening program; a new online referral test for familial CRC risk identification and referral advice; and a study on how to improve the genetic counselling process for individuals with a high familial CRC risk.

THESIS OUTLINE

This thesis contains the results of the RISCO study (risk of colorectal cancer), which was performed to improve the identification and referral of CRC patients and their relatives with an increased familial risk by clinicians in the Netherlands, and enhance informed choice of preventive measures by patients. In this chapter **(chapter 1)**, a general introduction on familial CRC risk identification and preventive measures is provided, as well as the rationale for this thesis.

The first step in any improvement process is to evaluate the current situation. This is done to find clues for improvement strategies, and to provide baseline measurements against which the effectiveness of such improvement strategies can be compared. In the first section of this thesis, the current situation regarding the identification and referral of individuals with an increased familial CRC risk was explored in two different settings (figure 1): CRC patients seen by a hospital clinician (gastroenterologist and/or surgeon) and healthy individuals participating in the pilot population screening program.

Chapter 2 contains a study which was performed in eighteen community hospitals to measure familial CRC risk identification and referral for preventive measures of CRC patients in clinical practice. Additionally, it contains a national cohort study which was performed to assess doctors' knowledge, which is known to play an important role in the identification and referral of individuals with an increased familial CRC risk.

Chapter 3 addresses another option for identifying individuals with an increased familial CRC risk, namely the population screening program. In the Netherlands, this program will start in 2013. It is not yet known how many participants with a positive FOBT have an increased familial CRC risk, i.e. whether using this program to identify families with an increased CRC might be effective. Therefore, the prevalence of a positive family history of cancer and familial CRC risk in participants of a pilot screening program was assessed.

To improve identification and referral of individuals with an increased familial CRC risk, adequate risk assessment, interpretation and communication are very important. These items were chosen as the starting point for the second section of this thesis, in which different guideline implementation strategies were studied.

Chapter 4 contains the study protocol for the RISCO study, a clustered randomised controlled trial in which two implementation strategies of the hereditary CRC guideline are compared. These strategies focus on clinicians' familial CRC risk identification, interpretation, and communication, as well as patients' uptake of preventive measures.

In **chapter 5**, the development and pilot testing of one of the implementation tools is described, namely the RISCO website. This website contains information about familial CRC risk, risk calculation tools and a decision support intervention for patients with a high familial CRC risk.

The effect of the two implementation strategies on referral rates and uptake of preventive measures were evaluated in a clustered randomised controlled trial (RISCO study) described in **chapter 6**. To determine which elements of the implementation strategies were especially useful in improving guideline implementation, patients' and clinicians' experience with these elements were studied in a process evaluation.

Besides the implementation strategies described in chapters 4-6, an alternative approach to improve implementation of the hereditary CRC guideline was developed and evaluated. This alternative consists of a new online referral test, aimed at improving the identification and referral of individuals with a high familial CRC risk for genetic counselling. In **chapter 7**, the sensitivity and usability of this online referral test were assessed.

Once it has been established that the familial CRC risk is high (lifetime risk >15%), referral for genetic counselling is recommended. It is vital that the counselling is optimal, because satisfaction with genetic counselling has been shown to improve adherence to surveillance recommendations. Therefore, counselees' information needs and preferences regarding the content, process and communication at the familial cancer clinic were studied to determine how the genetic counselling process may be further improved. This study is reported in **chapter 8**.

Finally, a general discussion on familial CRC prevention and future perspectives is presented in **chapter 9**.

REFERENCES

1. Järvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
2. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
3. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl.
4. Overbeek L, et al. Most patients with colorectal tumours at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008;51:1249-1254.
5. Van Dijk D, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 2007;6:131–134.
6. Foo W, et al. Family history? The forgotten question in high-risk colorectal cancer patients. Colorectal Dis 2009;11:450–455.
7. Alberto V, et al. Family and personal history in colorectal cancer patients: what are we missing? Colorectal Dis 2006;8:612-614.
8. Staal-Rosier P, et al. Inadequate referral for genetic evaluations of patients with colorectal carcinoma. Neth J Med 2009;153:124-128.
9. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
10. Singh H, et al. Underdiagnosis of Lynch syndrome involves more than family history criteria. Clin Gastroenterol Hepatol 2010;8:523–529.
11. Wong C, et al. Value of database linkage: are patients at risk of familial colorectal cancer being referred for genetic counselling and testing? Int Med J 2008;38:328–333.
12. Umar A, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268.
13. Arditi C, et al. Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. Endosc 2009;41:200-208.
14. Cairns SR, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-689.
15. Winawer S, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterol 2003;124:544-560.
16. Health Council of The Netherlands. A national colorectal cancer screening programme; 2009. Publication no.2009/13E.
17. Johns L, et al. A systematic review and metaanalysis of familial colorectal cancer risk. Am J Gastroenterol 2001;96:2992–3003.
18. Samowitz W, et al. The colon cancer burden of genetically defined hereditary nonpolyposis colon cancer. Gastroenterol 2001;121:830–838.
19. Parry S, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut 2011;60:950-957.
20. De Vos tot Nederveen Cappel W, et al. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. Gut 2003;52:1752-1755.
21. Lindor N, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006;296:1507-1517.
22. Järvinen H, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 2009;27:4793-4797.

23. Ligtenberg M, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet 2009;41:112-117.

24. Kempers M, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol 2011;12:49–55.

25. Van der Post R, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. J Med Genet 2010;47:464-470.

26. Vasen H, et al. Cancer risk in families with Hereditary Nonpolyposis Colorectal Cancer diagnosed by mutation analysis. Gastroenterol 1996;110:1020–1027.

27. Aarnio M, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999;81:214–218.

28. Capelle L, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterol 2010;138:487–492.

29. Koornstra J, et al. Management of extracolonic tumours in patients with Lynch syndrome. Lancet Oncol 2009;10:400-408.

30. Bonadona V, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304-2310.

31. Senter L, et al. The clinical phenotype of Lynch syndrome due to germline PMS2 mutations. Gastroenterol 2008;135:419–428.

32. Vasen H, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol 2001;19:4074-4080.

33. Hendriks Y, et al. Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterol 2004;27:17-25.

34. Plaschke J, et al. Lower incidence of colorectal cancer and later age of disease onset in 27 families with pathogenic MSH6 germline mutations compared with families with MLH1 or MSH2 mutations: the German Hereditary Nonpolyposis Colorectal Cancer Consortium. J Clin Oncol 2004;22:4486-4494.

35. Buttin B, et al. Penetrance and expressivity of MSH6 germline mutations in seven kindreds not ascertained by family history. Am J Hum Genet 2004;74:1262-1269.

36. Engel C, et al. Risks of less common cancers in proven mutation carriers with Lynch syndrome. J Clin Oncol 2012;30.

37. Vasen H, et al. Familial colorectal cancer risk: ESMO clinical recommendations. Ann Oncol 2009;20 Suppl 4:51-53.

38. Stupart D, et al. Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. Colorectal Dis 2009;11:126–130.

39. Vasen H, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. Gastroenterol 2010;138:2300–2306.

40. Jover R, et al. The efficacy of adjuvant chemotherapy with 5-fluorouracil in colorectal cancer depends on the mismatch repair status. Eur J Cancer 2009;45:365-373.

41. Lynch H, et al. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932.

42. De Jong A, et al. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64:367-370.

43. Burt R. Colon cancer screening. Gastroenterol 2000;119:837-853.

44. Kerber R, et al. Frequency of familial colon cancer and hereditary nonpolyposis colorectal cancer (Lynch syndrome) in a large population database. Fam Cancer 2005;4:239-244.

45. Kievit W, et al. Cost effectiveness of a new strategy to identify HNPCC patients. Gut 2005;54:97-102.

46. Manders P, et al. Young age and a positive family history of colorectal cancer are complementary selection criteria for the identification of Lynch syndrome. Eur J Cancer 2011;47:1407-1413.

47. Tranø G, et al. Performance of clinical guidelines compared with molecular tumour screening methods in identifying possible Lynch syndrome among colorectal cancer patients: a Norwegian population-based study. Br J Cancer 2010;102:482-488.

48. Sjursen W, et al. Current clinical criteria for Lynch syndrome are not sensitive enough to identify MSH6 mutation carriers. J Med Genet 2010;47:579-585.

49. Steinhagen E, et al. Systematic immunohistochemistry screening for Lynch syndrome in early age-of-onset colorectal cancer patients undergoing surgical resection. J Am Coll Surg 2012;214:61-67.

50. Julié C, et al. Identification in daily practice of patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer): revised Bethesda guidelines-based approach versus molecular screening. Am J Gastroenterol 2008;103:2825-2835.

51. Overbeek L, et al. Electronic reminders for pathologists promote recognition of patients at risk for Lynch syndrome: cluster-randomised controlled trial. Virchows Arch 2010;456:653-659.

52. Van Lier M, et al. Underutilization of microsatellite instability analysis in colorectal cancer patients at high risk for Lynch syndrome. Scand J Gastroenterol 2009;44:600-604.

53. Griffith K, et al. Influence of family history and preventive health behaviors on colorectal cancer screening in African Americans. Cancer 2008;113:276-285.

54. Hes F. Lynch syndrome: still not a familiar picture. World J Surg Oncol 2008;6:21.

55. Vadaparampil S, et al. Knowledge about hereditary colorectal cancer among colorectal cancer survivors. Genet Test Mol Biomarkers 2010;14:603-609.

56. Tranø G, et al. Awareness of heredity in colorectal cancer patients is insufficient among clinicians: a Norwegian population-based study. Colorectal Dis 2009;11:456-461.

57. Ready K, et al. Obstetrics/gynecology residents' knowledge of hereditary breast and ovarian cancer and Lynch syndrome. J Cancer Educ 2010;25:401-404.

58. Viana D, et al. Family history of cancer in Brazil: is it being used? Fam Cancer 2008;7:229-232.

59. Williams G, et al. Cancer genetics clinics and the surgeon: a valuable role for family history screening. Ann R Coll Surg Engl 2007;89:127–129.

60. Mak T, et al. Familial colorectal cancer referral to regional genetics department--a single centre experience. Fam Cancer 2007;6:81-87.

61. Aktan-Collan K, et al. Sharing genetic risk with next generation: mutation-positive parents' communication with their offspring in Lynch Syndrome. Fam Cancer 2011;10:43-50.

62. Stoffel E, et al. Sharing genetic test results in Lynch syndrome: communication with close and distant relatives. Clin Gastroenterol Hepatol 2008;6:333-338.

63. Ishii N, et al. Factors affecting encouragement of relatives among families with Lynch syndrome to seek medical assessment. Fam Cancer 2011;10:649-654.

64. Lawsin C, et al. An examination of the psychosocial factors influencing colorectal cancer patients' communication of colorectal cancer patient risk with their siblings. Cancer Epidemiol Biomarkers Prev 2009;18:2907-2912.

65. Bleiker E, et al. Screening behavior of individuals at high risk for colorectal cancer. Gastroenterology 2005;128:280-287.

66. Taylor D, et al. Comparison of compliance for colorectal cancer screening and surveillance by colonoscopy based on risk. Genet Med 2011;13:737-743.

67. Keller M, et al. Acceptance of and attitude toward genetic testing for hereditary nonpolyposis colorectal cancer: a comparison of participants and nonparticipants in genetic counseling. Dis Colon Rectum 2004;47:153-162.

68. Armelao F, et al. High uptake of colonoscopy in first-degree relatives of patients with colorectal cancer in a healthcare region: a population-based, prospective study. Endoscopy 2010;42:15-21.

69. Wollersheim H, et al. Clinical guidelines to improve patient care. Neth J Med 2005;63:188-192.

70. Boivin A, et al. Patient and public involvement in clinical guidelines: international experiences and future perspectives. Qual Saf Health Care 2010;19:e22.

71. National Institute for Health and Clinical Excellence (March 2012) The guidelines manual. London: National Institute for Health and Clinical Excellence. http://www.nice.org.uk.

72. Grol R. Beliefs and evidence in changing clinical practice. BMJ 1997;315:418-421.

73. Pavlidis N. Evidence-based medicine: development and implementation of guidelines in oncology. Eur J Cancer 2009;45 Suppl 1:468-470.

74. Woolf S, et al. Potential benefits, limitations, and harms of clinical guidelines. BMJ 1999;318:527–530.

75. Grimshaw J, et al. Implementing clinical guidelines: current evidence and future implications. J Contin Educ Health Prof 2004;24(Suppl1):S31-S37.

76. Grol R, Wensing M. Implementatie: Effectieve verbetering in de patiëntenzorg. 4e druk, 2012.

SECTION 1

CURRENT SITUATION

I'm preaching this sermon to show it ain't necessarily so

(Porgy and Bess)

Chapter 2

Familial colorectal cancer risk assessment in patients needs further improvement for more cancer prevention in relatives

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ABSTRACT

Aims: Previous data indicate that 12-30% of colorectal cancer (CRC) patients and relatives with an increased familial risk are referred for preventive surveillance. New guidelines recommend genetic counselling for high-risk families, and surveillance colonoscopies for moderate-risk families. In the present study, familial risk of CRC and referral rates for these preventive measures were determined one year after introduction of the new guidelines.

Methods: Assessment of familial risk of CRC and referral for preventive measures were studied among CRC patients (n=358) attending eighteen hospitals using medical records and questionnaires. Additionally, a knowledge survey was performed among clinicians.

Results: Sixty five (67%) of 97 patients with increased familial risk and 61 (23%) of 261 with low risk were referred for preventive measures. Uptake of genetic counselling in high-risk families was 33% (n=12/36). Uptake of surveillance colonoscopy in moderate-risk families was 34% (n=21/61). In the knowledge survey, clinicians correctly determined familial risk in 55% of ten cases and preventive measures in 65%.

Conclusion: Currently, 67% of individuals with an increased familial risk of CRC is referred for preventive measures. Only one-third of increased-risk families is referred in accordance with guidelines. To further enhance efficacy of cancer prevention, clinician education may be useful.

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INTRODUCTION

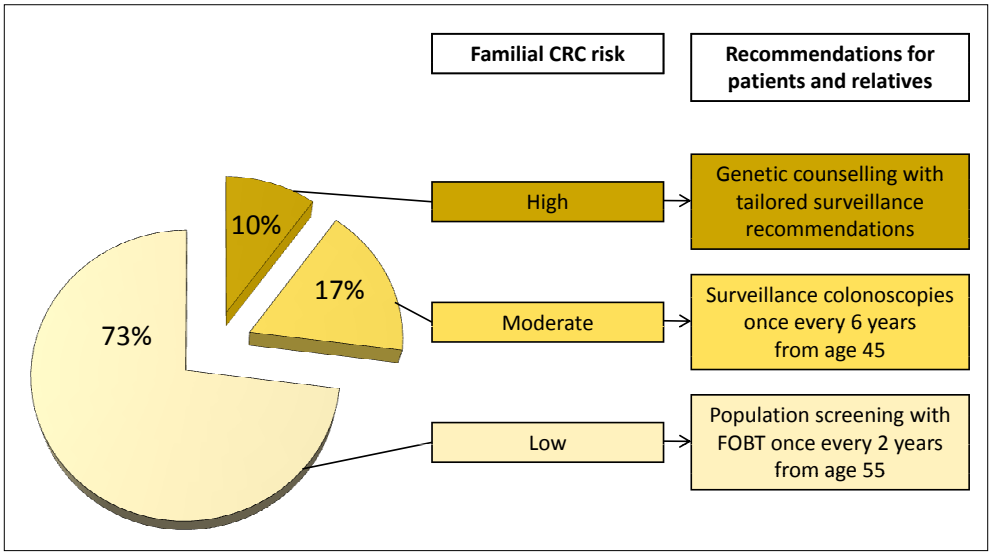
Familial or hereditary factors cause approximately 15-30% of all colorectal cancers (CRC).[1] This includes families with multiple affected relatives and/or relatives with early-onset CRC, in which healthy relatives have an increased familial risk of CRC, and affected relatives have an increased risk of metachronous cancers.[2,3] International guidelines recommend surveillance colonoscopies for these at-risk individuals, which reduce CRC-related morbidity and mortality by 43-80% and 65-81%, respectively.[4-9] However, 70-88% of individuals with an increased familial risk of CRC are not referred for these highly effective preventive measures.[10-13]

The familial risk level is important to determine which preventive measures are indicated. As shown in table 1 and figure 1, familial risk is generally divided into three categories: low (cumulative lifetime risk of CRC below 10%); moderate (10-15%); and high (exceeding 15%).[7-9,14] For low-risk individuals, population screening with faecal occult blood testing is recommended.[9] For moderate-risk families, surveillance colonoscopies every 3-6 years from age 40-50 are recommended.[6-9,14] Genetic counselling is recommended for CRC patients and their relatives with a high familial risk of CRC.[6-9,14] A clinical geneticist then determines whether a hereditary CRC syndrome is present. Lynch syndrome, previously referred to as Hereditary Non-Polyposis Colorectal Cancer or HNPCC, is the most common form of hereditary CRC. Lynch syndrome mutation carriers have high cumulative lifetime risks of CRC and endometrial cancer of up to 80%, and increased risks of other Lynch syndrome associated tumours (LSAT), such as ovarian and gastric cancer.[6-9,14-15] Surveillance recommendations include colonoscopies every 1-2 years from age 25, and gynaecological surveillance from age 30-35. Other hereditary CRC syndromes, such as familial adenomatous polyposis, are rarer and are disregarded in this paper.

For effective cancer prevention, it is vital to identify families with an increased risk of CRC and refer them for surveillance colonoscopies or genetic counselling, and not refer families at low risk. After assessment of familial risk and preventive measures, clinicians must discuss these with their patients, who are asked to share this information with their relatives. Previous studies have shown acceptance rates of genetic counselling between 26-93%, while uptake of surveillance colonoscopies was 48-83%.[16-21] Although insurance coverage plays an important role in some countries, these costs are fully reimbursed by compulsory healthcare insurance in the Netherlands.[22]

Prior research has shown that many clinicians lack knowledge regarding familial risk of CRC and preventive measures, resulting in low referral rates of 12-30%.[6-9,23-24] An evidence-based guideline on hereditary CRC was therefore developed in the Netherlands in 2008.[6-9,14] Because familial CRC risk assessment and communication are new concepts for many clinicians, we hypothesized that lack of knowledge may be an important barrier to guideline implementation. The current study was performed 1) to measure assessment and communication of familial risk of CRC and referral for preventive measures in clinical practice and 2) to assess clinicians' knowledge of familial risk of CRC and preventive measures, one year after publication of the new guideline.

Figure 1. Recommended preventive measures by familial risk of colorectal cancer category



In figure 1, the familial risk of colorectal cancer is shown in combination with the corresponding recommendations for colorectal cancer patients and their relatives. In our study, 10% of colorectal cancer patients had a high familial risk of colorectal cancer, 17% a moderate familial risk of colorectal cancer, and 73% a low familial risk of colorectal cancer.
CRC = colorectal cancer; FOBT = faecal occult blood test

Table 1. Categorization of familial risk of colorectal cancer

Familial risk of colorectal cancer (CRC) based on the Dutch guidelines on hereditary colorectal cancer.[14] Individuals not meeting any of these criteria have a low familial risk of colorectal cancer (<10% cumulative lifetime risk).

High familial risk of CRC (>15%), indication for genetic counselling
Healthy individual or patient with MSI negative CRC and: • First-degree relative with CRC or endometrial cancer before age 50 • Three or more (first- or second degree) relatives with CRC or LSAT before age 70 • Mismatch repair gene mutation in the family • MSI positive tumour
Patient with CRC and: • Age at diagnosis below age 50 • First-degree relative with CRC or LSAT before age 50 • Second CRC before age 70 • CRC and LSAT before age 70 • Two or more (first- or second degree) relatives with CRC or LSAT before age 70
Patient with colorectal adenoma with high-grade dysplasia before age 40
Patient with endometrial carcinoma before age 50
Moderate familial risk of CRC (10-15%), indication for surveillance colonoscopy every 3-6 years from age 45-50 but no genetic counselling
• Exclusion of hereditary CRC and diagnosis of familial CRC by a clinical geneticist • Two first-degree relatives with CRC between age 50-70 • A first-degree relative with CRC between age 50-70 and a second-degree relative with CRC before age 70 • A first-degree relative with an MSI negative CRC before age 50

First-degree relatives = parents, siblings and children; LSAT = Lynch syndrome associated tumours (i.e. malignancies of the endometrium, ovaries, stomach, small bowel, bile ducts, upper urinary tract and sebaceous glands); MSI = microsatellite instability; Second degree relatives = grandparents, aunts, uncles, nieces, nephews, grandchildren

METHODS

Study design and setting

Practice measurements were performed retrospectively among CRC patients and clinicians to measure assessment and communication of familial risk of CRC and preventive measures (surveillance colonoscopy and genetic counselling), and the uptake of these measures in clinical practice. Secondly, theoretical knowledge of familial risk of CRC and preventive measures was assessed in a national cohort study among clinicians.

Practice measurements

Patients and clinicians

CRC patients and their clinicians (surgeons and gastroenterologists) from eighteen Dutch community hospitals participated in the practice measurements. All patients newly diagnosed with colorectal adenocarcinoma before age 70 years between January 1st and July 31st 2009 were selected by the hospitals. Patients with previously known hereditary CRC were excluded. All patients received an information letter with an informed consent form and a questionnaire, signed by their clinician or the local study coordinator. Non-responders were mailed one reminder.

Patient baseline data including age, gender, and personal cancer history were collected retrospectively from medical records. Ethnicity, educational level and previous medical training were collected from questionnaires. Clinicians completed a questionnaire shortly before the start of the study providing baseline data on specialization and experience.

Assessment of familial risk of CRC

Questionnaires and medical records were used to determine whether a family history of cancer was taken. If positive, the number of affected relatives, type of cancer (CRC, LSAT, or other), age at diagnosis and level of kinship were recorded. From patient questionnaires, family history was assessed for first-degree relatives (parents, siblings, and children) only. Formal familial risk of CRC and corresponding preventive measures were determined by one of the researchers (ND), using family history and microsatellite instability (MSI) test results on tumour tissue where available. A positive MSI test indicated a high risk for Lynch syndrome, the most common form of hereditary CRC. MSI testing was indicated in patients with CRC before age 50 years or a second CRC before age 70.[14]

These formal familial risks of CRC (table 1) were based on criteria for MSI testing and the guideline criteria for referral for surveillance colonoscopy (for moderate risk of familial CRC) and genetic counselling (for high risk).[14] Patients meeting the criteria for MSI testing in whom this was not performed, were scored as having a high formal familial risk of CRC.

Endpoints

The endpoints were defined as follows:

- *Familial risk of CRC assessed:* Familial risk of CRC mentioned in medical records, or communication of the familial risk according to the patient questionnaire.
- *Familial risk of CRC correct:* Familial risk of CRC from medical records or patient questionnaires equal to the formal risk.
- *Preventive measures determined:* Preventive measures (genetic counselling or surveillance colonoscopies, or explicitly no measures) mentioned in medical records and/or patient questionnaires. Recommendations for surveillance colonoscopy

for CRC patients themselves were not included, since they will be in follow-up for several years after diagnosis, and are not yet eligible for surveillance colonoscopy for their increased familial risk.

- *Prevention recommendations correct:* Recommendations for preventive measures equal to formal measures: genetic counselling for a high familial risk of CRC; surveillance colonoscopy for a moderate familial risk of CRC; and no measures for a low familial risk of CRC.
- *Uptake of prevention:* For high familial risk of CRC patients: confirmation from a familial cancer clinic or the patient questionnaire that the patient had attended genetic counselling for CRC. For moderate familial risk of CRC patients: report in the patient questionnaire that their first-degree relatives had undergone one or more colonoscopy. For low familial risk of CRC patients: not having undergone these preventive measures.
- *Willingness to undergo preventive measures:* This was determined from patient questionnaires by asking whether patients would want to attend genetic counselling, or whether their relatives would want to undergo surveillance colonoscopy upon clinicians' recommendations.

Statistical analysis

Descriptive statistics were used to present baseline data. Baseline data and endpoints were compared between different formal familial risk in CRC categories (high/moderate/low and increased/low) using univariate analysis of variance (ANOVA), logistic regression and Pearson's Chi-square test. Significance was set at $p<0.05$. All statistical analyses were performed using SPSS v16.0.

Knowledge survey

Clinicians

All surgeons and gastroenterologists (including those in training), clinical oncogeneticists, and clinical geneticists in training from the Netherlands, and general practitioners (GPs) from the Nijmegen University Network of General Practitioners were invited to participate in a theoretical knowledge survey. The survey test version consisted of seven clinical cases (four high, one moderate, and two low familial risk of CRC), based on referral criteria for preventive measures.[14] All cases described a fictitious patient and included information on the number of times they had had CRC (1-2), the number of CRC-affected relatives (0-3) and age at diagnosis. Twenty-three oncogeneticists and genetic counsellors reviewed the survey. Based on their suggestions, MSI test results were added to the cases, where applicable. The final survey was web-based and consisted of ten cases (four high-, four moderate- and two low familial risk of CRC). Clinicians assessed familial risk of CRC and preventive measures for

each case. Baseline variables were collected in the survey and included specialisation, age, gender, experience and whether in training or not.

Statistical analysis

Data from clinicians who completed at least one case were included. Baseline variables are presented using descriptive statistics and compared between different familial risk of CRC categories (high/moderate/low and increased/low) using univariate ANOVA. Scores for familial risk of CRC and preventive measures were compared between clinicians using multivariate ANOVA. The influence of baseline variables on the scores were analyzed using univariate logistic regression. Significance was set at $p \leq 0.05$. All statistical analyses were performed using SPSS v16.0.

RESULTS

Practice measurements

Patients and clinicians

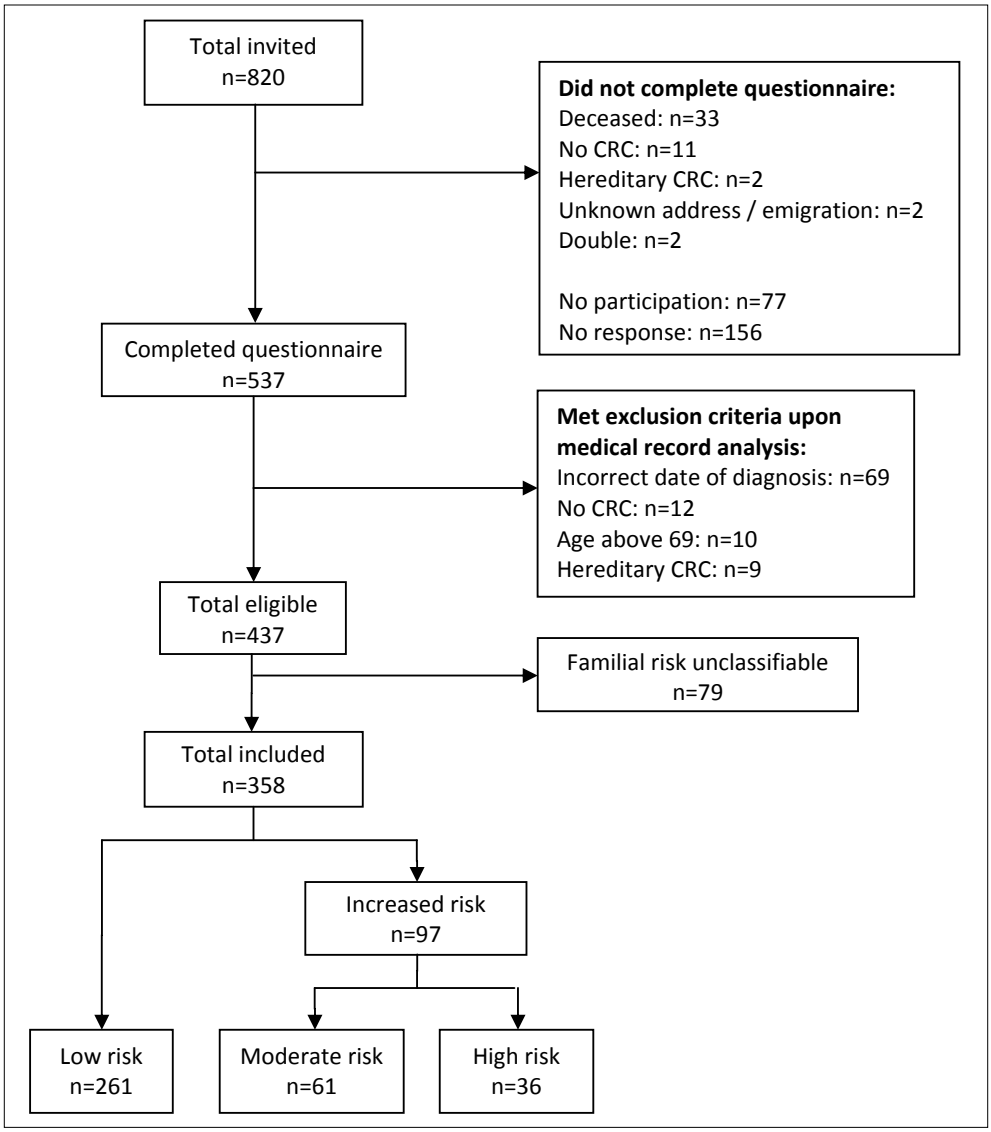
Seventy three surgeons and 64 gastroenterologists participated. Of these, 50 (36%) completed a questionnaire. Their median age was 44 years (31-61) years; 36 clinicians (72%) were men. Their median experience was 9 (0-30) years.

537 (65%) of 820 CRC patients completed a questionnaire. Another 100 patients (12%) met exclusion criteria during medical record analysis, mainly because their date of diagnosis did not fall within the study period (figure 2). Data on family history and MSI results were not reported in the medical records of another 79 (10%) patients, making it impossible to determine their formal familial risk of CRC. Baseline data of the 358 (44%) participating CRC patients are shown in table 2. Overall 60% (n=216) were male. Their median age was 61 (25-69) years. Patients with an increased familial risk of CRC were significantly younger than low-risk patients (54 vs. 61 years, $p<0.001$). Nearly all (99%) patients were Dutch.

Familial risk of CRC

A family history was obtained in 348 (80%) patients. MSI testing was performed in 44 (67%) of 66 patients meeting the criteria for MSI testing.[14] Combining family history and MSI results, the risk of CRC was high in 36 (10%) patients, moderate in 61 (17%), and low in 261 (73%). The level of familial risk of CRC determined from the questionnaire equalled 47 (56%) of 84 patients who reported their risk level in the questionnaire.

Figure 2. Flowchart of patient inclusion and familial risk stratification



In figure 2, the inclusion pathway and familial risk stratification of colorectal cancer patients in the clinical practice measures are shown.
CRC = colorectal cancer

Table 2. Baseline characteristics of 358 colorectal cancer patients by familial risk of colorectal cancer category

Baseline characteristics of 358 colorectal cancer patients whose data were available for familial risk stratification. Totals do not always add up to 100% due to missing data and/or rounding off.

Familial risk of CRC category		High n=36		Moderate n=61		Low n=261	
Determinant		**n**	**% / SD**	**n**	**% / SD**	**n**	**% / SD**
Gender	Male	23	64%	34	56%	159	61%
Age at diagnosis (years)	Mean	55.1	11.7	53.9	10.7	61.0	5.3
Educational level							
	Low	13	36%	17	28%	88	34%
	Medium	15	42%	25	41%	110	42%
	High	7	19%	17	28%	62	24%
Previous medical training		1	3%	6	10%	12	5%
Personal history of previous cancer							
	Any cancer	17	47%	13	21%	28	11%
	Second CRC	12	33%	8	13%	0	0%
	LSAT	4	11%	0	0%	0	0%
	Other cancer	1	3%	6	10%	28	11%
TNM stage							
	I	7	19%	11	18%	40	15%
	II	11	31%	19	31%	83	32%
	III	13	36%	21	34%	95	36%
	IV	4	11%	8	13%	37	14%
	Unknown	1	3%	2	3%	6	2%
Tumour location (proximal)		11	31%	11	18%	61	23%
Family history of cancer							
	Any cancer	20	56%	43	70%	112	43%
	CRC	12	33%	39	64%	52	20%
	LSAT	3	8%	2	3%	14	5%
	Other cancer	10	28%	16	26%	64	25%

CRC = colorectal cancer; LSAT = Lynch syndrome associated tumours (i.e. malignancy of the endometrium, ovaries, stomach, small bowel, bile ducts, upper urinary tract and sebaceous glands); SD = standard deviation; TNM = pathological staging of tumour size and invasion, lymph nodes and metastasis

Preventive measures

Preventive measures were taken by 67% of CRC patients with an increased familial risk of CRC (n=65/97) (figure 3, table 3). Genetic counselling was recommended to one-third of patients with a high familial risk of CRC (n=12/36). Eight of these and another four patients in addition (33%) had attended genetic counselling. Twenty-nine (81%) high-risk patients wanted to be referred for genetic counselling if recommended by their clinician.

Surveillance colonoscopy for relatives were recommended to 31 (51%) of 61 patients with a moderate familial risk of CRC. Uptake of surveillance colonoscopy was 34% (n=21/61) in relatives of patients with a moderate familial risk of CRC. Forty-three (70%) patients with a moderate familial risk reported that their relatives would want to undergo surveillance colonoscopy if recommended by their clinician.

Overall, measures were in accordance with guidelines in 233 (66%) of 358 CRC patients.[14] For genetic counselling, this was 12 (23%) of 53 and for surveillance colonoscopy, 21 (29%) of 73. Seventy-seven percent (200/261) of low familial risk of CRC patients were not referred. The guideline recommendations were therefore followed significantly more often in patients with a low familial risk of CRC compared with those with an increased familial risk (33 of 97, 34%) (p<0.001).[14]

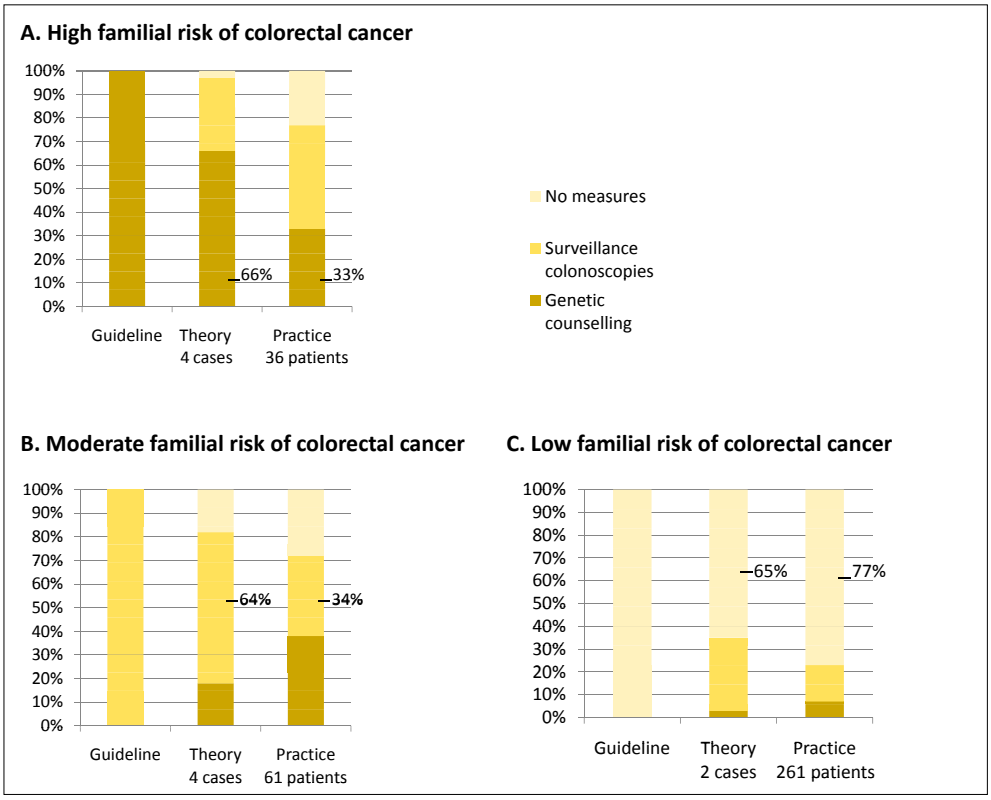
Table 3. Endpoint in 358 colorectal cancer patients by familial risk of colorectal cancer category

Outcome of familial risk assessment, communication and referral for preventive measures for 358 colorectal cancer patients whose data were available for familial risk stratification. Preventive measures in accordance with guidelines are shown in bold and underlined.

	High n=36		Moderate n=61		Low n=261	
	n	%	n	%	n	%
Clinicians						
Familial risk of CRC assessed						
Family history taken	33	92%	59	97%	261	100%
MSI-test performed	11	31%	39	64%	12	5%
Familial risk of CRC communicated	18	50%	37	61%	48	18%
Advice given for						
Genetic counselling	**12**	**33%**	27	44%	19	7%
Surveillance colonoscopies	16	44%	**31**	**51%**	41	16%
Patients						
Uptake of						
Genetic counselling	**12**	**33%**	23	38%	18	7%
Surveillance colonoscopies	9	25%	**21**	**34%**	43	16%

CRC = colorectal cancer; MSI = microsatellite instability

Figure 3. Results from the national knowledge survey versus actual uptake of preventive measures in clinical practice



In figure 3, referral for preventive measures is shown for colorectal cancer patients with A) high familial risk of colorectal cancer, B) moderate familial risk of colorectal cancer, and C) low familial risk of colorectal cancer. The left columns depict referral advice in accordance with guidelines: genetic counselling for a high risk, surveillance colonoscopies for a moderate risk, and no measures for a low familial risk of colorectal cancer. The middle columns depict clinicians' advice in a national theoretical knowledge survey. The columns on the right depict actual uptake of these preventive measures by 358 colorectal cancer patients in clinical practice.

Knowledge survey

Clinicians

2,169 clinicians were invited to participate in the knowledge survey, of whom 312 (14%) completed at least one case. They included 144 surgeons, 89 gastroenterologists, 37 clinical geneticists and 39 general practitioners. Three clinicians did not state their speciality. Two hundred (64%) were male and the median age was 42 (25-64) years; 91 (29%) were in training. The median duration of clinical experience was 6 (0-37) years.

Assessment of familial risk of CRC

Familial risk of CRC was correctly assessed in 55% of cases (table 4). Risk assessment was better for low (77% correct answers) than moderate (44% correct answers, p=0.005) and high familial risk (54% correct answers, p<0.001). Familial risk of CRC was underestimated in 43% of individuals at increased familial risk. Clinicians' characteristics such as speciality, age, gender, experience and being in training did not significantly influence these scores.

Preventive measures

Preventive measures determined by clinicians were in line with guidelines in 65% of all cases and 66% of increased familial risk of CRC cases (table 4 and figure 3). Clinical geneticists correctly determined preventive measures in 82% of cases, compared with 58% of surgeons (p=0.012). This did not differ significantly from gastroenterologists (69%) or GPs (62%). Age, gender, experience and being in training did not significantly influence these scores.

Table 4. Assessment of the theoretical knowledge survey among 312 clinicians

Clinicians' referral advice in ten fictional cases in a theoretical knowledge survey. Familial risk of colorectal cancer levels was high, moderate, or low. Preventive measures in accordance with guidelines are shown in bold and underlined.

Case	Familial risk of CRC	%	Clinicians' advice	%
High risk (4 cases)	Underestimated	46%	No measures	3%
	Correct	54%	Surveillance colonoscopies	31%
	Overestimated	NA	**Genetic counselling**	**66%**
Moderate risk (4 cases)	Underestimated	39%	No measures	18%
	Correct	44%	**Surveillance colonoscopies**	**64%**
	Overestimated	17%	Genetic counselling	18%
Low risk (2 cases)	Underestimated	NA	**No measures**	**65%**
	Correct	77%	Surveillance colonoscopies	32%
	Overestimated	23%	Genetic counselling	3%
Total	**Correct**	**55%**	**In accordance with guidelines**	**65%**

CRC=colorectal cancer; NA=not applicable

DISCUSSION

One year after publication of a guideline on hereditary colorectal cancer, two-thirds of families with an increased familial risk of CRC underwent preventive measures.[14] Referral was in accordance with guidelines in one-third of increased familial risk of CRC patients, while 23% of patients with a low familial risk of CRC were referred for preventive measures without indication.

While a family history was taken in 80% of patients, familial risk of CRC was discussed by the clinician with only 57% of members of families at increased risk of CRC. This shows that the assessment, interpretation and communication of the familial risk need to be embedded in clinical practice. This may be achieved by appointing a well-trained healthcare professional to be responsible for familial risk assessment for all CRC patients and who would discuss the familial risk and any preventive measures required. Incorporating this into local protocols could improve the assessment of familial risk and serve as a reminder for clinicians to discuss familial risk and preventive measures with their patients.

Relatives in one-third of moderate familial risk of CRC families underwent surveillance colonoscopy, while willingness to undergo this investigation was twice as high. This may be for several reasons. Actual willingness and uptake may be lower than the reported data, since CRC patients reported this for their relatives, and it is known that relatives do not always inform each other that they had a colonoscopy.[26] Unfortunately, directly approaching such relatives was not possible in our study for ethical reasons. Furthermore, both clinicians and patients may not realise that siblings have an increased familial risk of CRC. They think that only the children of the patient are at risk, and surveillance colonoscopy may not be discussed since the children are often too young. Also, not everyone follows surveillance recommendations, as colonoscopy uptake in relatives ranged from 48-83% in previous studies.[16-18]

Only one third of all referrals for preventive measures in CRC patients with an increased familial risk was in accordance with the guidelines. The absolute number of patients at increased familial risk referred for preventive measures is roughly equal to the number referred with a low familial risk, for whom these measures are not indicated. Both underuse and overuse of preventive measures has a significant impact on patients and their relatives and may lead to the inefficient use of resources and unnecessary costs.

Since the response rate of the clinicians was low, conclusions regarding their knowledge should be drawn with caution. They seemed to be more aware of preventive measures than the criteria for referral. Previous studies have shown comparable results. Thus, 26-75% of clinicians recommended genetic counselling in individuals at high familial risk of CRC.[24,25,27,28] Selection bias cannot be excluded, as clinicians interested in genetics may have been more willing to participate in the survey. Tailored paper and digital materials to further improve clinicians' knowledge of familial risk of CRC assessment and preventive measures are currently being tested in a randomised controlled trial.[28]

A main strength of this study is the use of mixed methods, as this gives a better view of actual practice. Generally, more information is communicated to the individual than is reported in the medical record. Another strength is the fact that a national sample of clinicians from multiple specialties involved in the care for CRC patients assessed the familial risk of CRC and preventive measures of realistic clinical cases. Unfortunately however, the participation was low in both the knowledge survey and the practice measurements. Clinicians may be reluctant to complete questionnaires for research purposes owing to their workload.[29] Furthermore, the survey could not be sent to gastrointestinal and oncologic surgeons specifically but it was sent to all surgeons, who do not all treat CRC patients. Thus, the actual participation rate was higher among surgeons.

Another limitation of the study is that 19% of CRC patients were invited to participate despite meeting the exclusion criteria, generally due to registration errors. Participation was, however, high (65%) in the 670 patients who fulfilled the inclusion criteria. In some instances the familial risk may not have been assessed until one to two years after diagnosis, despite the recommendation in the guidelines that this should be done immediately after diagnosis.[14]

In conclusion, the study showed that two-thirds of CRC patients and their relatives with an increased familial risk of CRC were referred for preventive measures. Half of these referrals were in accordance with the guidelines, while one quarter of patients with a low familial risk of CRC underwent preventive measures not indicated by the guidelines. Improving assessment of familial risk of CRC and referral for genetic counselling and surveillance colonoscopy can be accomplished by referring fewer CRC patients and relatives with a low familial risk and by improving the distinction between moderate and high risk. This will increase the efficacy of the process as fewer patients will be referred unnecessarily and lead to better cancer prevention of patients and their relatives with an increased familial risk of CRC in accordance with international guidelines.

REFERENCES

1. Lynch H, et al. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932.
2. Netherlands Cancer Statistics. http:///www.iknl.nl.
3. Siegel R, et al. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
4. Järvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
5. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
6. Vasen H, et al. Familial colorectal cancer risk: ESMO clinical recommendations. Ann Oncol 2009;20S4:51-53.
7. Arditi C, et al. Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. Endosc 2009;41:200-208.
8. Cairns S, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-689.
9. Winawer S, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterol 2003;124:544-560.
10. Overbeek L, et al. Most patients with colorectal tumors at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008;51:1249-1254.
11. Foo W, et al. Family history? The forgotten question in high-risk colorectal cancer patients. Colorectal Dis 2009;11:450-455.
12. van Dijk D, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 2007;6:131-134.
13. Staal-Rosier P, et al. Inadequate referral for genetic evaluations of patients with colorectal carcinoma. Neth J Med 2009;153:124-128.
14. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl
15. Vasen H, et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. Gastroenterol 1996;110:1020-1027.
16. Armelao F, et al. High uptake of colonoscopy in first-degree relatives of patients with colorectal cancer in a healthcare region: a population-based, prospective study. Endosc 2010;42:15-21.
17. Bleiker E, et al. Screening behavior of individuals at high risk for colorectal cancer. Gastroenterol 2005;128:280-287.
18. Taylor D, et al. Comparison of compliance for colorectal cancer screening and surveillance by colonoscopy based on risk. Genet Med 2011;13:737-743.
19. Keller M, et al. Acceptance of and attitude toward genetic testing for hereditary nonpolyposis colorectal cancer: a comparison of participants and nonparticipants in genetic counseling. Dis Colon Rectum 2004;47:153-162.
20. Holloway S, et al. Inequality of use of cancer genetics services by members of breast, ovarian and colorectal cancer families in South East Scotland. Fam Cancer 2008;7:259-264.
21. Loader S, et al. Patient vs. physician as the target of educational outreach about screening for an inherited susceptibility to colorectal cancer. Genet Test 2002;6:281-290.
22. Rolnick S, et al. Barriers in identification and referral to genetic counseling for familial cancer risk: the perspective of genetic service providers. J Genet Couns 2011;20:314-322.
23. Batra S, et al. Awareness of genetic testing for colorectal cancer predisposition among specialists in gastroenterology. Am J Gastroenterol 2002;97:729-733.

24. Schroy P 3rd, et al. Family history and colorectal cancer screening: a survey of physician knowledge and practice patterns. Am J Gastroenterol 2002;97:1031-1036.

25. Barrison A, et al. Colorectal cancer screening and familial risk: a survey of internal medicine residents' knowledge and practice patterns. Am J Gastroenterol 2003;98:1410-1416.

26. Jimenez J, et al. Physician-patient and patient-family communication after colonoscopy. Am J Gastroenterol 2012;107:1288-1295.

27. Schroy P 3rd, et al. A novel educational strategy to enhance internal medicine residents' familial colorectal cancer knowledge and risk assessment skills. Am J Gastroenterol 2005;100:677-684.

28. Dekker N, et al. Improving calculation, interpretation and communication of familial colorectal cancer risk: protocol for a randomized controlled trial. Implement Sci 2010;5:6.

29. Rosemann T, et al. General practitioners' attitudes towards research in primary care: qualitative results of a cross sectional study. BMC Fam Pract 2004;5:31.

Chapter 3

Adding familial risk assessment to FOBT can increase the effectiveness of population-based colorectal cancer screening

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ABSTRACT

Background: The Dutch Health Council recently recommended the introduction of a colorectal cancer (CRC) screening program by faecal occult blood testing (FOBT) for individuals aged 55-75 at population risk of CRC. Individuals at an increased familial CRC risk (≥ 2 times population risk) should be identified at a younger age, so they and their relatives can receive earlier, more intensive surveillance instead of FOBT.

Aims: To determine the percentage of participants with a positive FOBT in a CRC screening program with an increased familial CRC risk.

Methods: In a population-based study, 10,569 individuals aged 50-75 received an FOBT. Individuals with a positive FOBT were invited for colonoscopy and familial risk assessment. Participants with an average familial CRC risk were compared to those with an increased risk. Increased familial CRC risk was defined as a cumulative lifetime risk of CRC of at least 10%.

Results: Of 6,001 participants, 430 had a positive FOBT, of whom 324 (63% males; mean age 63 years) completed colonoscopy and familial risk assessment. CRC (n=22) and/or advanced adenomas (n=122) were found in 133 participants. Familial CRC risk was increased in 6% of participants with a positive FOBT. No significant differences were found between participants with an average versus an increased familial CRC risk.

Conclusion: Six percent of participants with a positive FOBT had an increased familial CRC risk. Identifying at-risk participants enables them and their relatives to undergo regular colonoscopies. Adding familial risk assessment to FOBT screening may thus prevent a substantial number of CRCs.

INTRODUCTION

In Western society, the lifetime risk of developing colorectal cancer (CRC) is 5-6%.[1-3] In concordance with advice by the European Union, the Health Council of the Netherlands recommended the introduction of a CRC screening programme for individuals aged 55-75, consisting of a biennial faecal occult blood test (FOBT), followed by colonoscopy in case of a positive FOBT.[4,5]

Familial and hereditary CRCs account for 15-20% of all CRCs.[6-8] De Jong et al found that 2.3% of the Dutch population had multiple relatives with CRC and/or a relative with CRC before the age of 50.[7] Members of these families have an increased familial CRC risk, i.e., a cumulative lifetime risk of developing CRC of at least 10%. According to international guidelines, these individuals should be identified at a younger age than the advised screening age of 55-75 years, to receive increased surveillance by regular colonoscopy.[9,10] Surveillance of moderate to high risk groups by regular colonoscopy significantly reduces the incidence of CRC and CRC-related mortality.[11,12] It is considered cost-effective to recommend a colonoscopy every 6 years from the age of 45 years to individuals with a moderate familial CRC risk of 10-15%.[9,10,13,14] For individuals with a high familial CRC risk above 15%, referral to a clinical geneticist is recommended for more precise risk assessment and determination of individualised preventive measures.[9,10,15]

However, many individuals with an increased familial CRC risk are still unidentified. If they are invited for population CRC screening, three scenarios can occur: 1) they decline to participate; 2) they have a negative FOBT; or 3) they have a positive FOBT. With the current design of the screening program, only participants with a positive FOBT are invited for colonoscopy and familial risk assessment. Thus, individuals with an increased familial CRC risk in the first two groups will remain unidentified as being high-risk. As a consequence, they cannot benefit from surveillance by regular colonoscopies; nor can their close relatives, who may also have an increased risk of developing CRC.

Two previous studies have assessed familial risk among participants in an FOBT screening program.[16,17] In both studies, familial CRC risk was assessed using questionnaires, which were sent along with the invitation for participation in the screening program. However, Navarro et al excluded individuals meeting criteria for Lynch syndrome, and only determined whether participants had a positive family history, defined as having a family member with CRC, endometrial or kidney cancer.[17] Worthley et al found that 4.2% of Australian participants had a familial CRC risk above 10%, warranting increased surveillance.[16] In the present study, familial risk assessment was performed among participants with a positive FOBT by

an experienced nurse or gastroenterologist to determine the percentage of – previously unidentified- participants in a Dutch CRC screening program who have an increased familial CRC risk.

METHODS

Study design and setting

From June 2006 to February 2007, a random sample of 10,569 individuals aged 50-75 in Nijmegen and surrounding areas were invited to a pilot CRC screening program. Individuals were randomised to receive either a guaiac-based FOBT (gFOBT) (Hemoccult II®) or an immunochemical FOBT (iFOBT) (OC-sensor®). This population-based study is described in detail elsewhere.[18]

Individuals with a positive FOBT were invited for colonoscopy. Everyone who accepted the invitation was seen by a specialised nurse or gastroenterologist who took a medical and family history, with the aid of a checklist. If the family history was positive for cancer, a more detailed pedigree was drawn.

Colonoscopy was performed by an experienced gastroenterologist. If possible, all observed neoplasms were removed, and other lesions were biopsied, if necessary. Histology was evaluated by an experienced pathologist. All colonoscopies were completed in May 2007.

The study was reviewed and approved by the Dutch Health Council. All participants gave written informed consent for the FOBT and, if applicable, for colonoscopy.

Data collection

From the checklists filled in during the visit and medical records, the following items were collected: demographic data (such as age and gender), FOBT results, pathology results, personal and family history of cancer, and possible confounders. Details and definitions are shown in table 1. Familial CRC risks were calculated from these data. Increased familial CRC risk was defined as a cumulative lifetime risk of CRC of at least 10%, i.e., a moderate or high familial CRC risk.[9]

Data analysis

Descriptive statistics were used to characterize the study population, family history and familial CRC risk. Age comparisons between the groups with true and false positive FOBTs were performed using independent samples T-tests (2-tailed). Gender (male/female), test type (iFOBT/gFOBT), personal and family history of any cancer/CRC/LSAT (yes/no) and possible signs of CRC, smoking and alcohol use (yes/no) were analysed as dichotomous

variables. These variables, as well as medication use (none/NSAIDs/anticoagulants/ combined use of NSAIDs and anticoagulants) and familial CRC risk categories (not increased [average] and increased [moderate or high]), were compared between participants with true and false positive FOBTs, and between participants with an average versus an increased familial CRC risk, using Pearson Chi-Square tests.
Significance was defined at the $p \leq 0.05$ level. All statistical analyses were performed using SPSS version 16.0.

RESULTS

Study population

Of the 10,569 participants, 57% (n=6,001) completed FOBT (Hemoccult® 51%, OC-Sensor® 62%) (figure 1). A positive FOBT was found in 430 participants (7%). The study population of the present study consists of the 324 participants with a positive FOBT (75%) who completed colonoscopy and familial risk assessment. The study population was predominantly male (63%) with a mean age of 63 years (SD 6.9) (table 2).
CRC (n=22) and/or advanced adenomas (n=122) were found in 133 participants. Thus, 41% of participants had a true positive FOBT. The remaining 191 individuals had a false positive FOBT, with minor adenomas (n= 77) and/or other pathology (n=81), or no pathology detected (n=55).
No significant relevant differences were found between participants with true versus false positive FOBTs.

Table 1. Variables measured in the study

Variable	Definition
FOBT results:	
True positive	CRC and/or advanced adenoma(s) upon colonoscopy
False positive	All other or no pathology upon colonoscopy
Pathology results:	
Colorectal carcinoma	Adenocarcinoma of the colorectum
Advanced adenoma	Adenomas ≥ 10 mm, with high-grade dysplasia or a villous component ≥ 20% [19]
Other lesions	Any lesions except for colorectal carcinoma or advanced adenoma (e.g., benign polyps, inflammations)
Personal history of:	
- Any cancer	Any malignant tumour
- CRC	Adenocarcinoma of the colorectum
- Definite LSAT	Epithelial ovarian carcinoma (including fallopian tube and primary peritoneal cancer), and malignancies of the endometrium, stomach, biliary tract, small intestine, upper urinary tract and benign and malignant tumours of the sebaceous glands [9]
- Possible LSAT	Abdominal tumours NOS, kidney tumours NOS, pancreatic cancer, and carcinomas of the brain and urinary bladder
Family history:	
Family size	The number of first-, second-, and third-degree relatives
Family history of CRC	CRC in first-, second-, and/or third-degree relatives
Family history of LSAT	LSAT in first-, second-, and/or third-degree relatives
Family history of other cancers	Other cancers than CRC or LSAT in first-, second-, and/or third-degree relatives
Familial CRC risk[a]:	
Average (CRC risk <10%)	Negative family history for CRC and LSAT; or one relative with CRC > 50 years
Moderate (CRC risk 10-15%)	One relative with CRC < 50 years, or two first- or second-degree relatives with CRC between 50-70 years
High (CRC risk >15%)	Meeting Amsterdam I/II or Bethesda criteria [9,15,20,21]
Confounders:	
Possible signs of CRC	Changed bowel habits, rectal blood loss[b], melena, abdominal pain, feeling of incomplete bowel movement, unintentional weight loss
Medication use	Use of NSAIDS and/or anticoagulants
Smoking	Smoking of any amount of tobacco-containing products
Alcohol use	Drinking of any amount of alcohol-containing beverages

CRC = colorectal cancer; FOBT = faecal occult blood test; LSAT = Lynch syndrome associated tumours; NOS = not otherwise specified; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs

[a] Familial CRC risk = cumulative lifetime risk of developing CRC

[b] Excluding bleeding from known haemorrhoids

Table 2. Baseline characteristics of 324 individuals with a positive FOBT in a CRC screening program

	False positive FOBT		True positive FOBT		Total	
	n	%	n	%	n	%
N of individuals (% of total)	191	59.0	133	41.0	324	100
Male gender	115	60.2	90	77.7	205	63.3
Mean age (SD)	62.1 (7.0)		63.4 (6.7)		62.6 (6.9)	
Number of iFOBTs (vs gFOBTs)*	173	90.6	108	81.2	281	86.7
Colonoscopy results†						
- CRC	0	0	22	16.5	22	6.8
- Advanced adenoma	0	0	122	91.7	122	37.7
- Minor adenoma	67	20.7	10	30.9	77	23.8
- Other pathology	59	30.9	22	16.5	81	25.0
- No pathology	55	28.8	0	0	55	17.0
Possible signs of CRC						
- Changed bowel habits	9	4.7	7	5.3	16	4.9
- Rectal blood loss#	19	10.0	24	18.0	43	13.3
- Melena	1	0.5	1	0.8	2	0.6
- Abdominal pain	14	7.3	8	6.0	22	6.8
- Feeling of incomplete bowel movement	9	4.7	7	5.3	16	4.9
- Unintentional weight loss	8	4.2	4	3.0	12	3.7
Medication use						
- NSAIDs	37	19.4	28	21.1	65	20.1
- Anticoagulants	7	3.7	2	1.5	9	2.8
Smoking	44	23.0	43	32.3	87	26.9
Alcohol use	153	80.1	102	76.7	255	78.7

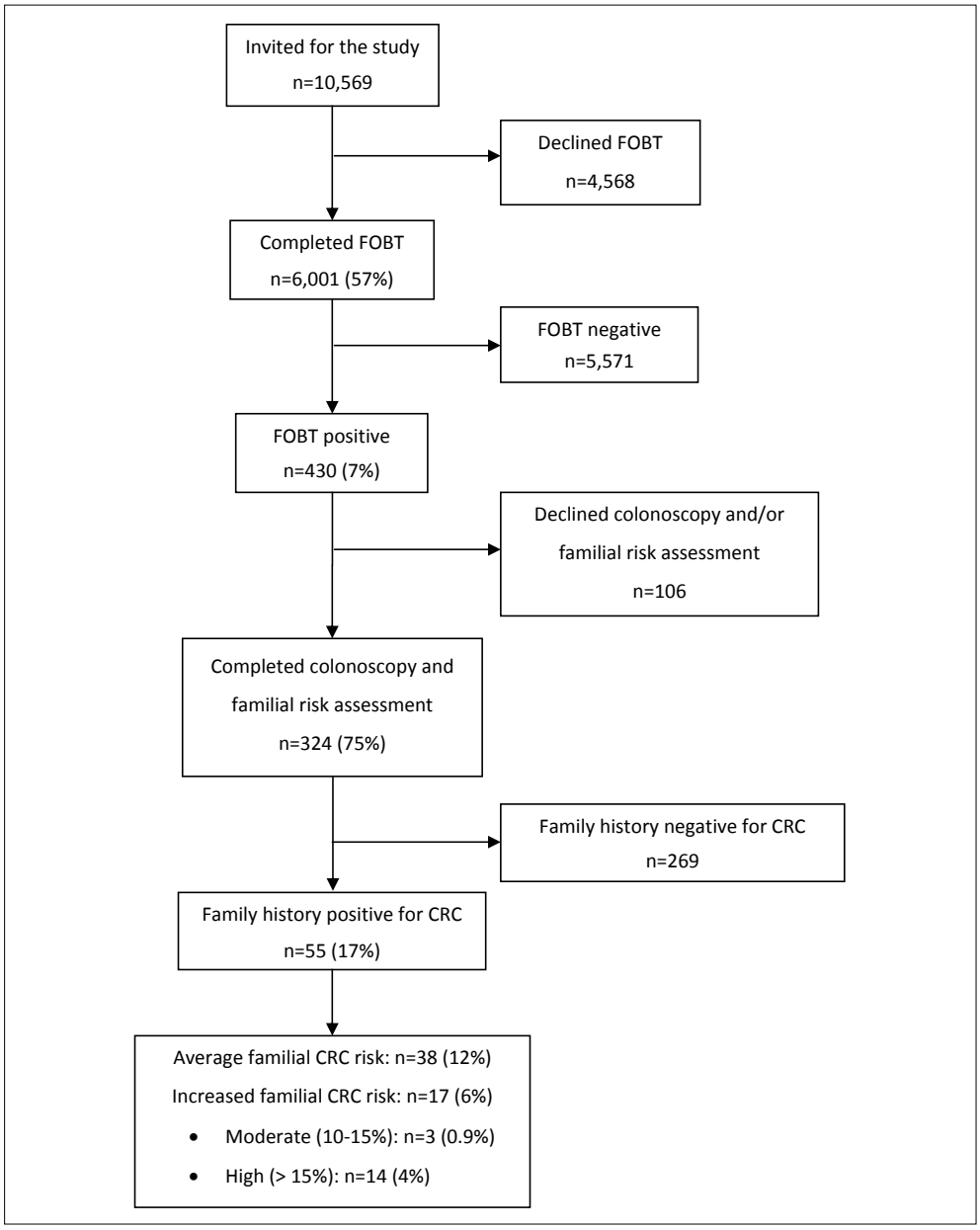
* p=0.021

† Results exceed 100%, since participants may have had more than one type of pathology

#Excluding bleeding from known haemorrhoids

CRC = colorectal cancer; FOBT = faecal occult blood test; gFOBT = guaiac-based FOBT; iFOBT = immunochemical FOBT; NA = not applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; SD = standard deviation

Figure 1. Flow chart from invitation to familial risk assessment



Average familial CRC risk = cumulative lifetime risk of developing colorectal cancer below 10%; CRC = colorectal cancer; FOBT = faecal occult blood test; Increased familial CRC risk: cumulative lifetime risk of developing colorectal cancer of at least 10%

Personal history of cancer

Details of personal and family history are shown in table 3. Approximately 10% of all participants reported a personal history of cancer (other than CRC and Lynch syndrome associated tumours). Three participants had a positive history of CRC or LSAT.

Family history of colorectal cancer

Information on family size was reported in pedigrees of 38 participants (12%) and in most cases, only included the number of brothers, sisters and/or children. One participant was adopted; no information on her biological relatives was known. Fifty-five participants (17%) had a positive family history of CRC; 36 with a false positive FOBT and 19 with a true positive FOBT.

Increased familial colorectal cancer risk

Six percent of participants had an increased familial CRC risk, i.e., a familial CRC risk above 10% (n=6 and n=11 among participants with true and false positive FOBTs, respectively). Familial CRC risk was above 15% in fourteen participants. In the other 38 participants with a positive family history of CRC, familial CRC risk was below 10%. No significant differences were found between participants with an average versus an increased familial CRC risk (data not shown).

Table 3. Personal and family history in 324 individuals with a positive FOBT in a CRC screening program

	False positive FOBT (n=191)		True positive FOBT (n=133)[a]		Total (n=324)	
	n	%	n	%	n	%
N of patients with personal history of:						
- Any cancer	14	7.3	18	13.5	32	9.9
- CRC/LSAT	1	0.5	2	1.5	3	0.9
N of patients with FH of CRC:						
- Positive FH of CRC	36	18.8	19	14.3	55	17.0
- ≥ 1 FDR with CRC	36	18.8	19	14.3	55	17.0
- ≥ 1 SDR with CRC	11	5.8	0	0	11	3.4
- Unknown[a]	0	0	1	0.8	1	0.3
N of patients with FH of definite/possible LSAT[b]:						
- Positive FH of LSAT	5	2.6	0	0	5	1.5
- ≥ 1 FDR with LSAT	5	2.6	0	0	5	1.5
- ≥ 1 SDR with LSAT	0	0	0	0	0	0
- Unknown[a]	0	0	1	0.8	1	0.3
N of patients with FH of other cancers:						
- Positive FH of cancer	15	7.9	5	3.8	20	6.2
- ≥ 1 FDR with cancer	15	7.9	5	3.8	20	6.2
- ≥ 1 SDR with cancer	1	0.5	0	0	1	0.3
- Unknown[a]	0	0	1	0.8	1	0.3
Familial CRC risk:						
- Average	180	94.2	126	94.7	306	94.4
- Moderate	2	1.0	1	0.8	3	0.9
- High	9	4.7	5	3.8	14	4.3
- Unknown[a]	0	0	1	0.8	1	0.3

[a] 1 missing: family history unknown because of adoption
[b] 3 definite, 2 possible
CRC = colorectal cancer; FDR = first degree relative; FH = family history; FOBT = faecal occult blood test; LSAT = Lynch syndrome associated tumours; Definite LSAT = epithelial ovarian carcinoma (including fallopian tube and primary peritoneal cancer), and malignancies of the endometrium, stomach, biliary tract, small intestine, upper urinary tract and benign and malignant tumours of the sebaceous glands; Possible LSAT = abdominal tumours not otherwise specified (NOS), kidney tumours NOS, pancreatic cancer, and carcinomas of the brain and urinary bladder; SDR = second degree relative

DISCUSSION

In this study, 17% of participants with a positive FOBT in a CRC screening program had a positive family history of CRC. Six percent of participants had a familial CRC risk of at least 10%. These prevalences are higher than previously reported in the general Dutch population by De Jong et al.[7] They performed a study among 5,072 Dutch individuals aged 45-70, who

filled in a questionnaire about the occurrence of CRC in their first-degree relatives (FDRs). Eleven percent of the 3,973 responders reported at least one FDR with CRC, while 2.3% of unaffected responders reported a FDR with CRC diagnosed before the age of 50, or two or more FDRs with CRC (i.e., a familial CRC risk above 10%). We cannot exclude that a positive family history of CRC is one of the reasons to participate in a screening program.[22] Also, advanced adenomas and CRCs might occur more often in participants with an increased familial CRC risk compared to those with a negative family history.[23,24] Since family history was not assessed in participants with a negative FOBT and decliners, the number of individuals with an increased familial CRC risk may therefore be higher in our study.

However, our results are in line with two other studies. First, an Australian study, where 19.6% of 2538 participants in an FOBT screening program reported a positive family history of CRC in a questionnaire.[16] Of these participants, 106 (4.2%) had a familial CRC risk high enough to warrant increased surveillance by colonoscopy rather than participation in a screening program. However, of the 377 participants with an increased familial CRC risk, only 28 (7.4%) had a positive gFOBT or iFOBT. In a Spanish study, 731 of 18,405 participants (4.9%) in a gFOBT screening program reported a positive family history, defined as having a family member with CRC, endometrial or kidney cancer.[17] Among those with a positive gFOBT, this percentage was 11.0%; 7.3% of participants with a negative gFOBT had a positive family history (p<0.005).

Strengths of our study include the assessment of family history by a small number of nurses and gastroenterologists who are very experienced in familial and hereditary CRC and all determined familial CRC risk as defined by the most recent guidelines.[9] Moreover, the large number of participants make for a good representation of the general population eligible for FOBT screening. A limitation of our study is that cancer diagnoses of relatives were not verified in medical records. The accuracy of a family history for CRC in first-degree relatives is very high, approximately 90%.[25,26] However, such accuracy is lower for second- and third-degree relatives, and for other cancer types, which can influence familial CRC risk. Since family history of colorectal cancer is correlated with family size, another limitation of our study could be that information about family size was mainly limited to first-degree relatives.[7] In addition, a quarter of all individuals with a positive FOBT did not complete colonoscopy and familial risk assessment, leading to a possible selection bias. We cannot be sure that no significant differences were present between individuals who underwent a colonoscopy and those who did not. Participants with a negative family history might feel that their risk of developing CRC is lower than in those with a positive family history and might therefore be less inclined to undergo colonoscopy and familial risk assessment.[22]

We estimated the number of CRCs that may be prevented by adding familial risk assessment to FOBT screening, based on the following assumptions. The first assumption is that the effectiveness of surveillance by regular colonoscopies in individuals with an increased familial CRC risk is identical to the effectiveness as described by Järvinen et al and Dove-Edwin et al.[11,12] In the study by Järvinen et al, 6% of high-risk participants undergoing surveillance developed CRC during the 15-year follow-up of the trial, compared to 16% of participants who did not undergo surveillance.[12] Dove-Edwin et al showed that the incidence of CRC was 43% lower in high-risk individuals, and 80% lower in participants with a moderate familial CRC risk, than the expected incidence in the absence of surveillance.[11] The second assumption is that participants have a mean number of three first-degree relatives (i.e., brothers, sisters and children) whose CRC risk is as high as that of the participant, and that these relatives do not yet participate in the screening program.[13] Based on these assumptions, an additional 172-184 CRCs may be prevented annually among participants with a positive FOBT and their relatives in the eligible Dutch screening population of 3.5 million individuals (with an expected uptake of 60%). This is just a tip of the iceberg, since many participants with a negative FOBT, as well as non-participants, also have an increased familial CRC risk.[16,17]

In conclusion, six percent of participants with a positive FOBT in a CRC screening program had a familial CRC risk above 10%. Although the FOBT screening program may serve as a way to identify these individuals, they should be referred for intensive surveillance by regular colonoscopies instead of participating in the FOBT screening program. Adding familial risk assessment to population screening with FOBT may therefore lead to the prevention of a substantial number of CRCs. Other methods are needed to assess familial CRC risk among non-participants.

REFERENCES

1. The Netherlands Cancer Registry and Statistics 1999-2008. http://www.iknl.nl
2. Jemal A, et al. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
3. Ferlay J, et al. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010;46:765-781.
4. European Commission. Cancer screening in the European Union: Report on the implementation of the Council Recommendation on cancer screening 2003.
5. Health Council of the Netherlands. A national colorectal cancer screening programme. Publication no.2009/13E.
6. Lynch H, et al. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932.
7. De Jong A, et al. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64:367-370.
8. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
9. Dutch Society for Clinical Genetics. Guideline Hereditary Colorectal Cancer 2008. Oisterwijk, 2008. http://www.oncoline.nl.
10. Vasen H, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 2007;44:353-362.
11. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
12. Järvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
13. Kievit W, et al. Cost effectiveness of a new strategy to identify HNPCC patients. Gut 2005;54:97-102.
14. Ramsey S, et al. A decision-analytic evaluation of the cost-effectiveness of family history-based colorectal cancer screening programs. Am J Gastroenterol 2010;105:1861-1869.
15. Arditi C, et al. Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. Endosc 2009;41:200-208.
16. Worthley D, et al. Many participants in fecal occult blood test population screening have a higher-than-average risk for colorectal cancer. Eur J Gastroenterol Hepatol 2006;18:1079-1083.
17. Navarro M, et al. Colorectal cancer screening: strategies to select populations with moderate risk for disease. Rev Esp Enferm Dig 2009;101:855-860.
18. Van Rossum L, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterol 2008;135:82-90.
19. Winawer S, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterol 2006;130:1872-1885.
20. Umar A, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268.
21. American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing. Gastroenterol 2001;121:195-197.
22. Hlavaty T, et al. Positive family history promotes participation in colorectal cancer screening. Bratisl Lek Listy 2005;106:318-323.
23. Boutron M, et al. Family history of colorectal tumours and implications for the adenoma-carcinoma sequence: a case control study. Gut 1995;37:830-834.

24. Butterworth A, et al. Relative and absolute risk of colorectal cancer for individuals with a family history: A meta-analysis. Eur J Cancer 2006;42:216-227.

25. Sijmons R, et al. Accuracy of family history of cancer: clinical genetic implications. Eur J Hum Genet 2000;8:181-186.

26. Ziogas A, et al. Validation of family history data in cancer family registries. Am J Prev Med 2003;24:190-198.

SECTION 2

IMPROVEMENT STRATEGIES

(Reid, Geleijnse & Van Tol)

Chapter 4

Improving calculation, interpretation and communication of familial colorectal cancer risk: Protocol for a randomized controlled trial

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ABSTRACT

Background: Individuals with multiple relatives with colorectal cancer (CRC) and/or a relative with early-onset CRC have an increased risk of developing CRC. They are eligible for preventive measures, such as surveillance by regular colonoscopy and/or genetic counselling. Currently, most at-risk individuals do not follow the indicated follow-up policy. In a new guideline on familial and hereditary CRC, clinicians have new tasks in calculating, interpreting, and communicating familial CRC risk. This will lead to better recognition of individuals at an increased familial CRC risk, enabling them to take effective preventive measures. This trial compares two implementation strategies (a common versus an intensive implementation strategy), focussing on clinicians' risk calculation, interpretation, and communication, as well as patients' uptake of the indicated follow-up policy.

Methods: A clustered randomized controlled trial including an effect, process, and cost evaluation will be conducted in eighteen hospitals. Nine hospitals in the control group will receive the common implementation strategy (*i.e.*, dissemination of the guideline). In the intervention group, an intensive implementation strategy will be introduced. Clinicians will receive education and tools for risk calculation, interpretation, and communication. Patients will also receive these tools, in addition to patient decision aids. The effect evaluation includes assessment of the number of patients for whom risk calculation, interpretation, and communication is performed correctly, and the number of patients following the indicated follow-up policy. The actual exposure to the implementation strategies and users' experiences will be assessed in the process evaluation. In a cost evaluation, the costs of the implementation strategies will be determined.

Discussion: The results of this study will help determine the most effective method as well as the costs of improving the recognition of individuals at an increased familial CRC risk. It will provide insight into the experiences of both patients and clinicians with these strategies. The knowledge gathered in this study can be used to improve the recognition of familial and hereditary CRC at both the national and international level, and will serve as an example to improve care for patients and their relatives worldwide. Our results may also be useful in improving healthcare in other diseases.

BACKGROUND

The lifetime risk of developing colorectal cancer (CRC) in Western society is 5 to 6%.[1,2] Familial and hereditary cancers account for approximately 15 to 20% of all CRCs.[3-5] In these families, healthy relatives of CRC patients may have an increased risk of developing CRC themselves. This so-called familial CRC risk can be divided into three groups, based on cumulative lifetime risks of developing CRC:

1. Average: familial CRC risk below 10%.
2. Moderate: familial CRC risk of 10-15%.
3. High: familial CRC risk above 15%.

For each group, a different follow-up policy applies. For individuals with an average familial CRC risk, neither surveillance nor genetic counselling is indicated. For individuals with a moderate familial CRC risk, surveillance by regular colonoscopy is indicated. For individuals with a high familial CRC risk, referral for genetic counselling is recommended. Identification of individuals with an increased familial CRC risk is crucial because surveillance significantly reduces CRC-related morbidity and mortality, by 43 to 80% and 65 to 81%, respectively.[6,7] Both underuse and overuse of surveillance and genetic counselling have a significant impact on patients and their relatives, and may lead to unnecessary costs.

Familial CRC risk is assessed by family history and, in a subset of patients, microsatellite instability (MSI) analysis performed by pathologists. Unfortunately, both procedures are difficult. Previous research has shown that patient family history often is missing or incomplete, and information provided by patients is not always accurate.[4,8-11] Furthermore, interpretation of the family history (determining the indicated follow-up policy) is not always correct.[12] Pathologists' selection of patients for MSI is often incomplete, while clinicians regularly interpret the results incorrectly.[13] Consequently, only 12 to 30% of CRC patients with a high familial CRC risk are referred for genetic counselling.[4,10,14-16] Other studies have shown that many CRC patients referred to a familial cancer clinic belong to an average or moderate risk population for whom genetic counselling is not indicated.[17,18]

Clinicians involved in the care for CRC patients recognize the need for improvement in this area. Therefore, a multidisciplinary evidence-based guideline on familial and hereditary colorectal cancer (FHCC) was launched in the Netherlands in 2008.[19] An important addition compared to previous national and international guidelines is that surgeons and gastroenterologists (referred to as 'clinicians' in this protocol) have new tasks in calculating, interpreting, and communicating familial CRC risk. Because clinicians are often unfamiliar with these tasks, implementation strategies are needed to ensure that patients and their

relatives receive proper counselling and follow-up.[15] In a previous trial, an electronic reminder system specifically aimed at pathologists improved completeness of patient selection for MSI testing.[13] In this trial, we will provide support at both clinician and patient level to further implement the guideline.

This trial compares two implementation strategies: a common strategy (*i.e.*, dissemination of the guideline) versus an intensive implementation strategy, focussing on clinicians' risk calculation, interpretation, and communication, as well as patients' uptake of the indicated follow-up policy. An effect, process, and cost evaluation will be performed. The improvement of the identification and referral of patients at an increased familial CRC risk will lead to a higher number of individuals following an appropriate surveillance program, thereby reducing CRC-related morbidity and mortality.

METHODS

Study design and setting

A clustered randomized controlled trial including an effect, process, and cost evaluation will be conducted in eighteen community hospitals. All patients with CRC diagnosed under the age of 70 years and their clinicians will be invited to participate. To prevent contamination bias, randomization will take place at hospital level. Stratification will take place according to hospital size (<500, 500 to 700, and >700 beds), and be performed by means of a computerized randomization system. This study was approved by the Committee on Research Involving Human Subjects of the region Arnhem-Nijmegen.

Primary objectives

This trial compares two implementation strategies: a common strategy versus an intensive implementation strategy, focussing on clinicians' risk calculation, interpretation, and communication, as well as patients' uptake of the indicated follow-up policy.

Hypothesis

Providing patients and clinicians with information on CRC, a risk assessment tool, risk communication aids, and decision aids will improve calculation, interpretation, and communication of the familial CRC risk by clinicians, as well as patients' uptake of the indicated follow-up policy more than dissemination of the guideline only.

Outcome measures

Effect evaluation

1. The percentage of CRC patients for whom a correct familial CRC risk is calculated by clinicians.
2. The percentage of CRC patients for whom a calculated familial CRC risk is correctly interpreted by clinicians.
3. The percentage of CRC patients with whom a calculated familial CRC risk and/or follow-up policy is communicated by clinicians.
4. Patients' uptake of the indicated follow-up policy.

Process evaluation

1. Actual exposure to the different elements of the implementation strategies.
2. The experiences of patients and clinicians with these elements.

Cost evaluation

Costs of the implementation strategies in relation to the number of correctly referred patients.

Participants

Clinicians from eighteen hospitals will participate. All their patients diagnosed with CRC under the age of 70 years during the six-month inclusion period are eligible for inclusion. Patients must be able to provide informed consent and be able to read and understand Dutch. Patients previously referred for genetic counselling for CRC are excluded. Patients will be selected by PALGA (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), the nationwide network and registry of histo- and cytopathology in the Netherlands.[20]

All patients will receive a patient information letter, signed by their treating clinician, along with an informed consent form. After signing the informed consent form, they will be included in the study.

Interventions

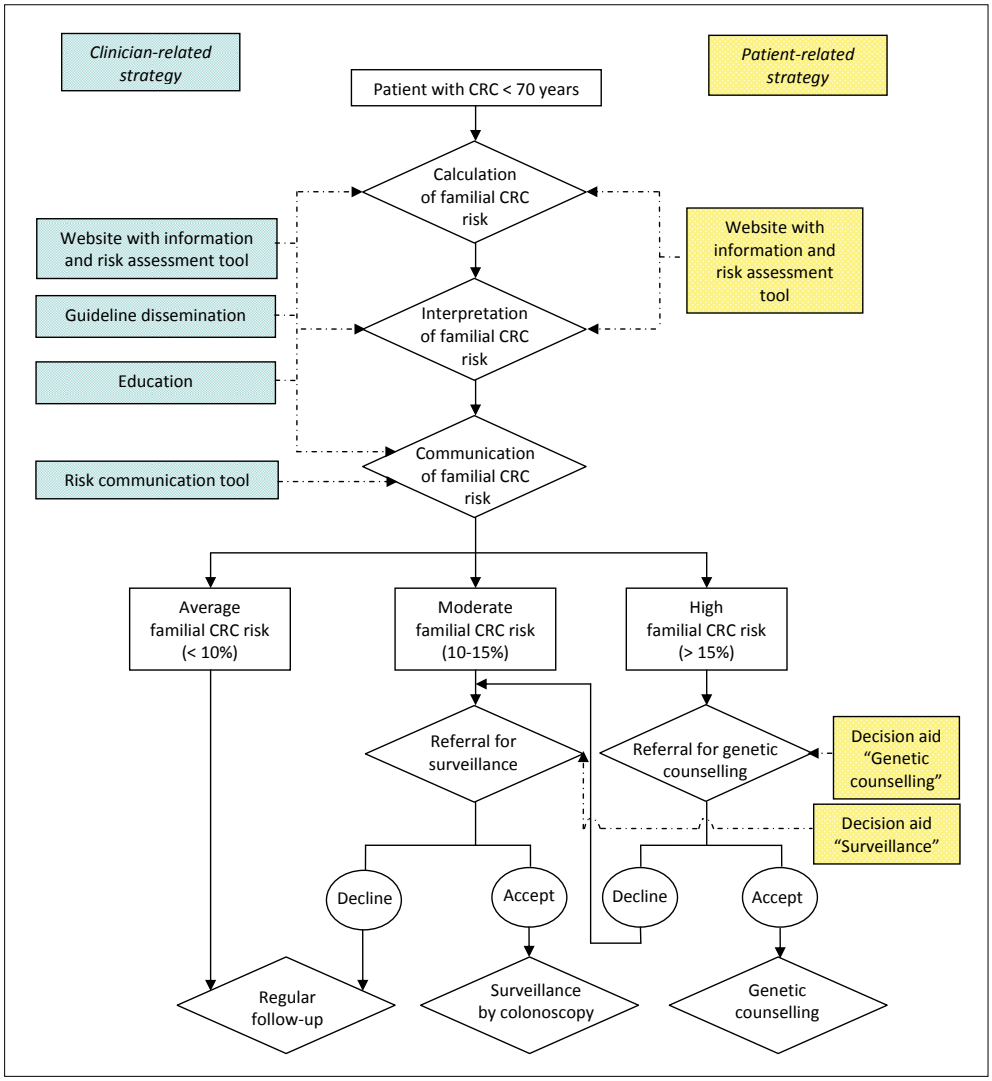
Implementation strategies in both groups

In both the control group and the intervention group, clinicians will receive the FHCC guideline.

Intensive implementation strategy in the intervention group

The intensive implementation strategy is summarized in figure 1 and consists of the following implementation tools: a website for patients and clinicians; education for clinicians; and a risk communication tool for clinicians.

Figure 1. Intensive implementation strategy for the intervention group, aimed at both patients and clinicians



The rhombuses in this figure represent the tasks clinicians have in calculation, interpretation and communication of the familial colorectal cancer (CRC) risk in CRC patients. It also shows the various elements of the intensive implementation strategy aimed at both patients and clinicians (in yellow and green, respectively) that will be compared to dissemination of the guideline on familial and hereditary colorectal cancer only.
Familial CRC risk: cumulative lifetime risk of developing CRC for first-degree relatives of CRC patients.

Website

The website consists of the following items:

1. A summary of evidence-based and relevant information about familial CRC risk (lifetime risk of developing CRC). Natural frequencies with the same denominator and visual displays will be used. Absolute risks will be presented, as well as in comparison to the population risk. The outcomes are offered in both positive and negative frames (*e.g.*, the risk of developing CRC as well as the chance of not developing CRC). The focus is on familial CRC risk and the different follow-up policies. The information is presented in two different formats, one for patients and one for clinicians.
2. A risk assessment tool to calculate patients' familial CRC risk. Patients fill in medical information about themselves and their relatives with regard to CRC and other cancers. Clinicians can use the tool as well. The calculated familial CRC risk is given in the same format as the rest of the website. Advice for follow-up is offered based on this risk, as well as a reminder to use the corresponding decision aid, if applicable.
3. Decision aids, aimed at facilitating decisions involving the uptake of the indicated follow-up policy (one for surveillance and one for genetic counselling). Tools supporting patients in making informed choices about their healthcare, such as decision aids, have been shown to improve knowledge, clarify preferences, and reduce uncertainty around decision making, with high levels of acceptability among consumers.[21,22] The decision aids used in this trial provide balanced information on different options, *i.e.*, to be referred for surveillance/genetic counselling or not. The following items are addressed: background information, benefits and harms, and the potential impact on the patient and their relatives. Worksheets are provided for patients to list and rate the importance of the benefits and harms for themselves.

The website is available exclusively to patients and clinicians in the intervention group. A login name and password will be provided upon inclusion. Patients can use the website independently before or after regular follow-up visits, and are encouraged to discuss the results with their clinician. They are instructed to keep the decision aid within their family, and not share it for reasons of research integrity. To minimize contamination bias, after the trial all patients in the control group will be asked if they were exposed to the website.

Education

In an educational meeting, clinicians in the intervention group will be trained to use the FHCC guideline.

Risk communication tool

Clinicians will receive a tool for communicating the familial CRC risk with their patients during a regular follow-up visit. The tool consists of written information and visual displays of the population risk of CRC, an explanation of the risk level of the patient and his/her relatives, as well as the indicated follow-up policy. It is designed in the same format as the website.

Development of the implementation tools

During development, the content and presentation of the website and the risk communication tool will be reviewed by physicians not specifically trained in genetics, and by non-medical personnel as well as representatives from the Dutch CRC patient associations (Vereniging HNPCC-Lynch and Stichting Doorgang). Improvements will be made based on their comments. Before use, the tools will be tested among approximately 20 patients and 20 clinicians. The purpose of this pilot is determining whether the website and the tools are acceptable, the information is presented clearly, and the completion of the tools is feasible.

Power calculation

To detect a difference of 20% between the intervention group and the control group in uptake of surveillance by colonoscopy in patients at moderate familial CRC risk, and referral for genetic counselling in patients at a high familial CRC risk, at least 186 patients are required (alpha=0.05, a two-sided testing and power=0.80). However, considering an intracluster-correlation coefficient of 0.15 and an average of five patients per clinician, at least sixty clinicians and 300 patients are needed. For eighteen hospitals this means three to four clinicians and 15 to 20 patients per hospital.

Data collection

Baseline characteristics

Baseline characteristics from patients, clinicians, and hospitals will be collected in the following manner:

1. Patients: From PALGA, data including age, gender, and some medical information will be collected. Medical information includes diagnoses of cancer (diagnosed since 1971), cancer type, and age at diagnosis, as well as the result of MSI testing. The following data will be collected by a self-administered questionnaire: ethnicity, current marital status, educational level, previous medical or health training, and family history of cancer (type of cancer and age at diagnosis). Family history is collected for first-degree relatives (*i.e.*, parents, siblings, and children).
2. Clinicians: All participating clinicians will be asked to provide baseline data (*e.g.*, specialization, number of years of experience) in a questionnaire.

3. Hospitals: From the hospitals' websites, characteristics such as size, teaching status, and presence of an outpatient department for genetic counselling will be obtained.

Effect evaluation

Before introducing the implementation strategies, a baseline assessment of risk calculation, interpretation, and communication will be performed. Both the baseline assessment and the evaluation of the implementation strategies will be performed retrospectively in the same manner. Baseline characteristics will be collected in the manner described above. The measuring instruments will be developed by identifying all relevant variables and translating these into questionnaires. When possible, existing validated questionnaires will be used.

The family history as reported by the patient in the questionnaire will be used to calculate a formal familial CRC risk and determine the indicated follow-up policy. This will be compared to the family history taken by the clinician, along with the risk calculation and interpretation performed by the clinician. These data will be extracted from the patients' medical records. The medical records will also be used to determine the number of patients with whom the familial CRC risk and corresponding follow-up policy has been communicated. To determine the number of referred patients who actually visit a familial cancer clinic, these clinics will be asked to report whether these patients have visited. The uptake of surveillance by colonoscopy by first-degree relatives will be determined by asking the patients whether their relatives are actually screened. Medical records and results from the decision aids on the website will be used to determine whether patients at an increased risk who were not referred for surveillance or genetic counselling were not referred because they had chosen not to be referred or because it was not discussed.

Process evaluation

In the process evaluation, data are collected on actual exposure of patients and clinicians to the different elements of the implementation strategies, as well as their experience with these elements:

1. Website: The website automatically records the following data when it is used: who used which elements; how often did users visit the different elements of the website; and how long did it take to use the different elements. By using questionnaires, users' experiences with the website will be ascertained.
2. Education: Attendance at the meetings will be determined by keeping an attendance list. The duration of the meetings will be recorded. In addition, clinicians' experience with the meetings will be ascertained by using a questionnaire.
3. Risk communication tool: Patients and clinicians will be asked whether the tool was used. Their experience with the tool will be measured using questionnaires focussing on the perceived usefulness and usability of the tool.

Cost evaluation

Costs accompanied with the development and implementation of the website and risk communication tool will be accounted for, as well as the costs for dissemination of the guideline. Clinicians will provide time estimates to use the different elements. Costs will be correlated to the number of correctly referred patients.

Data analysis

Effect evaluation

To analyze the effectiveness of both implementation strategies, descriptive statistics and multilevel analysis will be used. Patient, clinician, and hospital characteristics will be included in the multilevel analysis, allowing for correction of the effectiveness for probable differences in case mix between the different hospitals. The statistical analyses will be performed using SPSS version 16.0 for Windows.

The percentage of correctly referred patients is defined as follows:

1. The percentage of patients at an average familial CRC risk who are not referred for surveillance or genetic counselling.
2. The percentage of patients at a moderate familial CRC risk who want to be referred and are referred for surveillance.
3. The percentage of patients at a moderate familial CRC risk who do not want to be referred and are not referred for surveillance.
4. The percentage of patients at a high familial CRC risk who want to be referred and are referred for genetic counselling.
5. The percentage of patients at a high familial CRC risk who do not want to be referred and are not referred for genetic counselling but are referred for surveillance if they opt for it.
6. The percentage of patients at a high familial CRC risk who do not want to be referred and are not referred for genetic counselling or surveillance.

Process evaluation

Frequencies and means are used to assess the actual exposure of the patients and clinicians to the elements of the implementation strategies and to assess their experience with these elements. A multilevel regression analysis will be applied to assess which elements of the intensive implementation strategy were particularly associated with effective implementation of the new FHCC guideline.

Cost evaluation

The costs of implementation related resource use will be calculated on a per patient basis. The costs of the use of each element per correctly referred patient will be calculated. The costs of the intensive implementation strategy will be compared to the costs of dissemination of the guideline only.

DISCUSSION

Objectives

The aim of this trial is to compare two implementation strategies: a common implementation strategy (dissemination of the guideline only) versus an intensive implementation strategy, focussing on clinicians' risk calculation, interpretation, and communication, as well as patients' uptake of the indicated follow-up policy, such as referral for colonoscopy or genetic counselling.

Strengths and weaknesses

To our knowledge, this is the first study of an implementation strategy designed to improve the recognition of patients' familial CRC risk by addressing both patients and their clinicians (surgeons and gastroenterologists). If the intensive implementation strategy is successful, the elements (the website and the risk communication tool) can be released for general use by patients and clinicians. They may also serve as an example for other hereditary and non-hereditary diseases. Our study will add knowledge to the effectiveness of patient decision aids and the best way of supplying patients and clinicians with information on disease risks. Some limitations need to be addressed. Family history as reported by the clinician will be compared to the family history reported by the patient in a self-administered questionnaire. Previous research has shown that the accuracy of family history of CRC in first-degree relatives reported by patients is approximately 90%.[23] The optimal way of ensuring that the family history reported by the patient is accurate is by reviewing medical records of the affected relatives. Since written permission from relatives is needed to do so, this is not feasible and will therefore not be done in this study.

In our evaluation, only patients will be included; their relatives are not. Patients will be asked whether their relatives are screened, but the relatives will not be contacted to assess whether they actually received the results from the risk assessment and the matching advice.

Measurements may be contaminated in case others are provided with the login code for the website.

Collecting data from medical records does not monitor everything that is discussed between the clinician and the patient. This may lead to underestimation of the risk interpretation and communication. Videotaping the consultations would shed light on the content and quality of the risk communication, but would also influence the intervention by reminding the clinician of the intervention. In this study, regular clinical practice will be left undisturbed as much as possible.

Implications

The results of this study will help determine the most effective way of improving the recognition of individuals at an increased familial CRC risk. It will provide insight into the experiences of both patients and clinicians with these strategies.

This is important because many people are currently not treated according to evidence-based guidelines, and can benefit from proper cancer risk assessment and appropriate follow-up, which has been proven to reduce morbidity and mortality. The knowledge gathered in this study may improve the recognition of familial and hereditary CRC at national and international level and serve as an example to improve care for patients and their relatives worldwide. In addition, our results may be useful in improving healthcare in other diseases.

REFERENCES

1. The Netherlands Cancer Registry and Statistics 1999-2003: http://www.iknl.nl.
2. Jemal A, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-249.
3. Lynch H, et al. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932.
4. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
5. de Jong A, et al. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64:367-370.
6. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
7. Järvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
8. Sijmons R, et al. Accuracy of family history of cancer: clinical genetic implications. Eur J Hum Genet 2000;8:181-186.
9. Church J, et al. Family history of colorectal cancer: how often and how accurately is it recorded? Dis Colon Rectum 2000;43:1540-1544.
10. Foo W, et al. Family history? The forgotten question in high-risk colorectal cancer patients. Colorectal Dis 2009;11:450-455.
11. Ruo L, et al. Limitations of family cancer history assessment at initial surgical consultation. Dis Colon Rectum 2001;44:98-103.
12. Alberto V, et al. Family and personal history in colorectal cancer patients: what are we missing? Colorectal Dis 2006;8:612-614.
13. Overbeek L, et al. Electronic reminders for pathologists promote recognition of patients at risk for Lynch syndrome: cluster-randomised controlled trial. Virchows Arch 2010;456:653-659.
14. van Dijk D, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 2007;6:131-134.
15. Overbeek L, et al. Most patients with colorectal tumors at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008;51:1249-1254.
16. Staal-Rosier P, et al. Inadequate referral for genetic evaluations of patients with colorectal carcinoma. Neth J Med 2009;153:124-128.
17. Mak T, et al. Familial colorectal cancer referral to regional genetics department--a single centre experience. Fam Cancer 2007;6:81-87.
18. Williams G, et al. Cancer genetics clinics and the surgeon: a valuable role for family history screening. Ann R Coll Surg Engl 2007;89:127-129.
19. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl.
20. Casparie M, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol 2007;29:19-24.
21. Barratt A, et al. Use of decision aids to support informed choices about screening. BMJ 2004;329:507-510.
22. O'Connor A, et al. Decision aids for people facing health treatment or screening decisions. Cochr Datab Syst Rev 2003,CD001431.
23. Ziogas A, et al. Validation of family history data in cancer family registries. Am J Prev Med 2003;24:190-198.

Chapter 5

Stepwise optimisation of web-based interventions for familial colorectal cancer: participation of patients and clinicians

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Submitted for publication

ABSTRACT

Objective: To describe the stepwise optimisation of a website aimed at improving familial colorectal cancer risk calculation, interpretation and communication.

Design: Observational study.

Setting: University hospital in the Netherlands.

Participants: Colorectal cancer patients (n=20) and clinicians (n=12).

Intervention: A website with information on familial colorectal cancer, risk calculators for patients and clinicians and a decision support intervention for patients, based on scientific evidence and expert opinions.

Main outcome measures: Usability, understandability and perceived effectiveness of the website, and reasons for use.

Results: Pilot testing in two steps resulted in several improvements, particularly in the navigation and decision support intervention. After implementing these changes, users found the website easy to use and the information understandable. Patients and clinicians considered the website helpful in improving familial colorectal cancer risk calculation, interpretation and communication. Patients mainly wanted to use the website for information, while clinicians wanted to determine whether to refer their patients for preventive measures.

Conclusions: Pilot tests among patients and clinicians show that the website is easy to use, understandable and seems effective in improving familial colorectal cancer risk calculation, interpretation and communication. Using a stepwise approach made it possible to thoroughly evaluate the website with a limited number of users. It is important to include representatives from possible users in the development process, since their reasons to use the website differ. Wide-spread implementation of the website could improve quality of care for colorectal cancer patients and their relatives by enabling them to undergo highly effective cancer prevention.

INTRODUCTION

Surveillance colonoscopies in individuals with an increased familial colorectal cancer (CRC) risk reduce CRC-related morbidity and mortality with up to 80%.[1,2] To enable CRC patients and their relatives to take these highly effective preventive measures, clinicians need to calculate the familial risk, determine whether preventive measures are indicated, and communicate this with their patients, who are asked to share this information with their relatives. However, currently only 12-30% of individuals with an increased familial CRC risk are referred for preventive measures in accordance with international guidelines.[3-10]

Familial CRC risk is divided into three categories: high (i.e., a cumulative lifetime CRC risk of more than 15%), moderate (10-15%), and low (below 10%).[7,9,10] For high-risk families, genetic counselling is recommended. A clinical geneticist determines familial CRC risk and preventive measures for patients and their relatives, based on family history and DNA analysis. Less stringent surveillance is recommended for moderate-risk individuals: surveillance colonoscopies every six years, starting at age 45.[7] Individuals with a low familial CRC risk are advised to participate in population screening programs.

To improve referral of patients and relatives with an increased familial CRC risk, both patient-directed and clinician-directed education can be effective.[11] Supplying patients with information and decision support interventions can improve their knowledge and ability to discuss decisions regarding referral with their clinician.[12] Patients' knowledge and understanding are most effectively improved with tailored and interactive information, for which the Internet is an attractive option.[13] Many patients are interested in obtaining cancer information and support online, and approve of computerized tools for familial risk assessment.[14] A large number of clinicians use information and communication technologies in clinical practice, provided they are beneficial and easy to use.[15]

Thus, referral for surveillance colonoscopies and genetic counselling may be improved by providing CRC patients and clinicians with a website about familial CRC risk. Here we describe the pilot test of this website, which contains information, risk calculators, and a decision support intervention (DSI). Previous articles about development processes of similar tools emphasize the need for rigorous testing in several rounds.[16-18] Since this is not always practical, we used a stepwise approach in the pilot test of our website, implementing changes from a limited number of participants (4-8) before going to the next round of testing. In addition to assessment of the website's usability, understandability, perceived effectiveness, and reasons for use, we determined the effectiveness of this stepwise optimisation process.

METHODS

General development

The website was developed together with stakeholders in accordance with published frameworks.[16,17] During development, an expert panel provided their expertise on medical issues, patient communication and other issues. Subsequent versions were reviewed by representatives from patient associations and by clinical geneticists, genetic counsellors and other medical and non-medical personnel from the Radboud University Nijmegen Medical Centre (RUNMC). The website was available to users with a login code at http://www.risco-darmkanker.nl.

Description of the website

Information on familial CRC risk

The information on familial CRC risk was presented in separate formats for patients and clinicians. It was based on the Dutch guideline for hereditary colorectal cancer and additional literature.[7] Based on literature reviews and the views of our expert panel and the patient representatives, the information for patients contained information on general and familial CRC risk, surveillance colonoscopies and genetic counselling. The information for clinicians consisted of information on CRC risk, familial and hereditary CRC, including referral criteria for preventive measures.

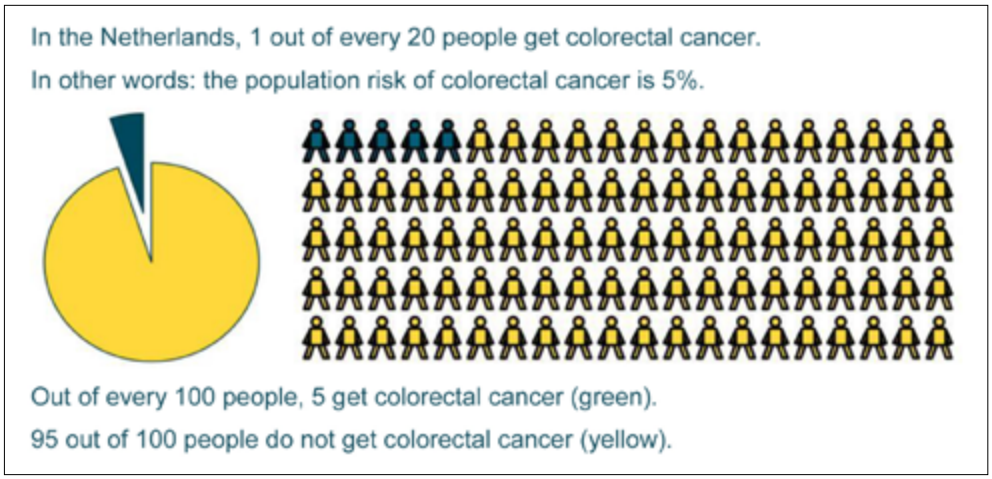
Much research has been done about how to optimise patients' understanding and risk perception.[13,19,20] Therefore, risks were presented in absolute frequencies and percentages, in both positive and negative frames. Risks were visualized using pie charts and pictographs (figure 1).

Risk calculators

Two separate familial CRC risk calculators were developed for patients and clinicians. Publicly available risk calculators were used as an inspiration to develop ours. Risk calculations were based on referral criteria for surveillance colonoscopies for moderate-risk families and genetic counselling for high-risk families.[7] To check whether the results were consistent with the input, the risk calculators were tested using scenarios representing all possible combinations of answers.

In the final versions, users entered information about cancer type and age at diagnosis for themselves and their first- and second-degree relatives. Cancer types included CRC and other tumours that influence familial CRC risk, such as endometrial and gastric cancer. Upon completion, familial CRC risk levels were given for the patient and their relatives, along with the corresponding advice (i.e., no measures, surveillance colonoscopies, or genetic counselling for a low, moderate and high familial CRC risk, respectively). Patients were encouraged to discuss these results with their clinician.

Figure 1. Example of risk visualization: population risk of colorectal cancer



Decision support intervention

Most high-risk CRC patients for whom genetic counselling is indicated, want to be referred.[21,22] Yet, since genetic counselling and testing can have negative psychosocial consequences, up to 20% of patients decline genetic counselling or have uncertainties regarding referral.[21] Therefore, a decision support intervention (DSI) was developed to help high-risk CRC patients elicit their values with regard to genetic counselling and make a personal decision whether or not to be referred. No DSI was developed for moderate-risk patients, as they will be in follow-up for at least five years after being diagnosed with CRC, and are not yet eligible for surveillance colonoscopies for their increased familial risk.

The DSI was based on available examples, the Ottawa Decision Support Framework and International Patient Decision Aids collaboration's checklist.[23,24] It consisted of five steps. First, patients were encouraged to read information on genetic counselling, which explicitly stated that not everyone knows whether they want to be referred. On page two, patients answered general questions on their risk perception and decision making preferences. Next, eight commonly named pros and cons of genetic counselling were provided, which were collected from literature and reviewed by patient representatives, clinical geneticists and genetic counsellors. Patients could add one or two attributes that were important to them personally. In step three, they ranked these attributes on a Likert scale (1=very important; 4=not important/not applicable). In step four, they were asked whether these items were reasons for them to be referred for genetic counselling or not. For example, for many people, receiving information on their risk of developing another cancer is a reason to attend genetic

counselling. However, this can be a reason to refrain from genetic counselling if one does not want to know this risk. Finally, patients identified the most important reason in step five. The answers from step three and four were combined on a Likert scale (1=very important reason not to be referred for genetic counselling; 7=very important reason to be referred for genetic counselling). The score from step five was doubled and added to the total score. If the patient's score was lower than the middle score, this means that they did not want to be referred (and vice versa). This was presented as follows: "Your answers indicate that you (want to / do not want to / do not yet know whether you want to) be referred for genetic counselling." Patients were encouraged to discuss this with their clinician.

Pilot test

In 2010-2011, a pilot test was performed to determine the website's usability, understandability of the information, perceived effectiveness of the risk calculators and the DSI, as well as reasons to use the website. Patients diagnosed with CRC below age 75 who visited the surgery outpatient department or the familial cancer clinic of the RUNMC were asked to participate by their surgeon, surgical nurse or one of the researchers (ND). Patients were asked to read all information on familial CRC risk and to use their risk calculator and the DSI, regardless of their familial CRC risk. Additionally, surgeons, gastroenterologists, and medical oncologists of the RUNMC reviewed the website. These clinicians were asked to read all information and use their risk calculator.

Users' opinions and recommendations for improvement were collected with think-aloud techniques, semi-structured interviews and questionnaires. Questions were asked about their general opinion, usability and lay-out of the website. Understandability and added value of the information was assessed. For the risk calculators and DSI, users' opinions were collected regarding ease of use and understandability of the results. Time needed to complete the risk calculators was measured, and perceived effectiveness was determined by asking users whether it provided more insight into the familial CRC risk. For the DSI, perceived effectiveness in supporting decision making regarding referral for genetic counselling was assessed.

Users were invited for the pilot test until no more new suggestions for improvement were made. Technical problems were solved immediately; other changes were made after approximately one-third of potential users had reviewed the website, before going to the next revision round. The website was finalized using the recommendations of all users.

RESULTS

Baseline characteristics

Thirty-four colorectal cancer patients were invited to participate in the pilot test. Twenty of them (59%) participated: nine women and eleven men. Median age was 60 years (range: 41-71 years); all patients were of Dutch ancestry. Patients had been diagnosed with CRC 1-175 months previously (median: 22 months). Eight patients had finished higher education. Familial CRC risk was distributed as follows: six low, six moderate, and eight high risk.

All twelve invited clinicians participated in the pilot test: seven surgeons, three medical oncologists and two gastroenterologists. Eight clinicians were men; median age was 45 years (range: 36-57 years). Clinicians had been working as an attending clinician for 2-21 years (median: 11 years) and treated between 1-100 new CRC patients each year (median: 24).

Pilot testing by patients

With a score of 7.5 on a scale of 1-10, CRC patients were generally positive about the website (table 1). This score was higher after implementing the adaptations from the first eight patients (7.3 vs. 7.7, respectively). Six of the first eight patients had problems with the navigation: it was not clear to them which information they had already read. Therefore, a contents page and an overview of the website were added. After these adjustments, users were much more positive about the navigation and could find their information more easily. Sixteen patients (80%) felt the website was an addition to the information they had received from their clinician. Patients were particularly interested in the risk factors for CRC, and would have liked more information in this area, particularly on dietary issues. Changes included minor textual changes as well as the addition of short patient testimonials to help users imagine what surveillance colonoscopies or genetic counselling might mean for them. As for the risk calculator, four of the first eight patients found it difficult to use and offered suggestions for improvement. After implementing these, the next twelve patients considered the risk calculator easy to use, and found the results clear and helpful in providing more insight into their familial CRC risk and preventive measures for themselves and their relatives. Patients completed the tool in 3-11 minutes (mean: 6 minutes).

Although patients were generally positive about the decision support intervention, several adjustments had to be made during the pilot test. For example, the question “How important are these attributes to you?” led most patients to think that they were asked to which extent they agreed with the item. Therefore, the sentence “For me, this is ...” was added to each item. This had the wanted effect: in the new version, patients considered whether the items were important to them personally. Also, since patients found it difficult to name one main reason for (not) wanting to be referred for genetic counselling, this was changed

into providing two main reasons. After implementing the adjustments, eight out of twelve patients found the DSI easy to use, and helpful in deciding whether or not to be referred for genetic counselling. The final version of step three of the DSI is shown in figure 2.
Patients mainly wanted to use the website to obtain more information and to review the information at their own convenience.

Table 1. Results from the pilot test of the website

Items	Questions	Patients n=20		Clinicians n=12	
		n / score	% / range	n / score	% / range
General opinion	Total score (1-10)	7.5	6-9	7.8	6-9
	Attractiveness	17	85%	8	67%
	Improved risk communication	ND		10	83%
	Use the website again	16	80%	12	100%
	Recommend to others				
	To patients	20	100%	11	92%
	To clinicians	ND		11	92%
Usability	Ease of use	16	80%	9	75%
	Ease of finding information	16	80%	8	67%
	Navigation	12	60%	7	58%
Layout	Clarity of information presentation	19	95%	10	83%
	Use of visual displays	18	90%	10	83%
Information on CRC	Added information / knowledge	16	80%	6	50%
	Understandability of information	19	95%	8	67%
Risk calculator	Ease of use	16	80%	9	75%
	Understandability of results	14	70%	9	75%
	More insight in familial CRC risk	15	75%	9	75%
Decision support intervention	Ease of use	11	55%	ND	
	Understandability of results	16	80%	ND	
	Helpfulness in decision making	12	60%	ND	

CRC = colorectal cancer; ND = not determined

Pilot testing by clinicians

As shown in table 1, clinicians were positive about the website, with a mean score of 7.8 out of 10. This score was higher after implementing the adaptations from the first four clinicians (7.0 vs. 8.3, respectively). Clinicians found the website useful to review information, and mainly wanted to use it to determine whether to refer their patients for preventive measures. Their suggestions for improvement included leaving out ten-year risks of developing CRC

and only using lifetime risks, as well as improving the clarity of the text and moving around information to make it easier to find.
All clinicians felt that the risk calculator helped them calculate and interpret their patients' familial CRC risk, completing the tool within 2-3 minutes, using an example of a patient with a positive family history of CRC.

Figure 2. Step three of the decision support intervention for genetic counselling

How important are the following reasons for you?

	Very important	Pretty important	A little important	Not important/ not applicable
I will receive extra information on my risk of developing cancer again. For me, this is...	◉	○	○	○
I will receive a personal surveillance advice. For me, this is...	◉	○	○	○
My family members will receive advice about their risk of colorectal cancer and possible surveillance. For me, this is...	◉	○	○	○
I will get more certainty about the cause of my colorectal cancer. For me, this is...	◉	○	○	○
Genetic counseling can lead to fear, stress and feelings of guilt. For me, this is...	◉	○	○	○
Being confronted with an increased risk of developing cancer for myself is unpleasant. For me, this is...	◉	○	○	○
Genetic counseling can lead to unpleasant reactions from family members. For me, this is...	◉	○	○	○
Being confronted with an increased risk of developing cancer for my family members is unpleasant. For me, this is...	◉	○	○	○
Other reason: [ ] For me, this is...	◉	○	○	○
Other reason: [ ] For me, this is...	◉	○	○	○

DISCUSSION

In this study, a website about familial colorectal cancer risk calculation, interpretation and communication was effectively optimised by following a two-step approach with a limited number of participants. Furthermore, we show the importance of involving users in the development of materials meant for them. While both patients and clinicians offered important suggestions for improvements, their reasons to use the website and therefore their suggestions for adjustments differed significantly. Patients mainly wanted to use the website to obtain information and to review it at their own convenience. In contrast, clinicians mainly wanted to use the website to determine whether or not to refer their patients for surveillance colonoscopies and/or genetic counselling. Adapting the website to users' needs and preferences is important, to ensure benefit for future users. Doing this in a stepwise manner resulted in a thoroughly tested website with limited resources and time, making it a very practical development method.

The framework used to develop our website, the Knowledge To Action framework, resembles the development process as described by Elwyn et al.[16,17] Among others, both recommend multiple review rounds by surrogate users. We show that a condensed form of this rigorous development process, with implementation of changes recommended by the first four to eight users, led to an effective optimisation of the website, with very positive judgments from the remaining participants. Users were invited until saturation was reached, in this case twenty patients and twelve clinicians in only two rounds, making this stepwise approach an attractive option for the development of future tools.

Our website enables CRC patients to find out whether they have an increased familial risk, and which preventive measures are indicated for them and their relatives. The information and the decision support intervention help patients to make a personal choice regarding referral for genetic counselling and participate in a more equal discussion with their healthcare provider. This may be an important manner to improve quality of care, which is necessary as currently only 12-30% of high-risk individuals are referred for preventive measures.[3-6]

One of the added values of our website over previous websites is that it combines information on familial CRC risk with risk calculators and a decision support intervention, suitable for both patients and clinicians. For example, Family Healthware™ is a self-administered, web-based tool that assesses familial risk for CRC and other common diseases, and provides a personalized prevention plan.[14,25] Some of their findings during usability testing were in line with our study, such as users skimming over texts instead of reading everything. However,

Family Healthware™ does not provide specific information on familial CRC risk, and assesses risk for six diseases, whereas our website focuses specifically on CRC. In addition, their tool does not take into account other tumours that may influence familial CRC risk, such as endometrial cancer. Another strength of our website is that it is aimed at all risk groups. Many organizations provide information on hereditary CRC, but none of them provide specific information for individuals with a moderate familial CRC risk.

Since our website contains is based on international evidence, it can easily be translated into English and other languages, reaching a large number of CRC patients and their relatives worldwide. However, it remains necessary to have the website evaluated by foreign patients, as all participants in our study were of Dutch descent. All foreign patients who were invited for the study declined, often because of an inability to understand Dutch.

The use of patient testimonials remains controversial. Some authors have shown that patient testimonials influence users in making a choice, since it is difficult to balance the information and present it in such a manner that users view all options.[26] Others find it helps patients in understanding their options, and how it may affect them if they choose one option or the other.[27] Based on patients' advice, we added short statements, derived from statements that patients gave during the pilot test. They were balanced to give both positive and negative views of surveillance colonoscopies and genetic counselling.

The website is currently being evaluated in a randomised controlled trial to determine its effect on familial CRC risk calculation, interpretation and communication in clinical practice.[28] If the website and other materials are effective in improving the recognition of individuals with an increased familial CRC risk, they will become publicly available. Furthermore, the website will be adapted for use in healthy individuals interested in their familial CRC risk.

In conclusion, we show that using a stepwise approach to optimise a website aimed at improving familial colorectal cancer risk calculation, interpretation and communication is an effective manner to easily optimise it with a limited number of surrogate users. It is important to include representatives from all possible users in the development process of similar instruments, since their reasons to use the website, and thus their suggestions for improvement, may differ. Pilot tests among patients and clinicians show that the website is easy to use, understandable and is perceived as effective. Wide-spread implementation of the website could improve the quality of care for colorectal cancer patients and their relatives worldwide by enabling them to take highly effective cancer prevention measures.

REFERENCES

1. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
2. Järvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
3. Overbeek L, et al. Most patients with colorectal tumors at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008;51:1249-1254.
4. Van Dijk D, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 2007;6:131-134.
5. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
6. Staal-Rosier P, et al. Inadequate referral for genetic evaluations of patients with colorectal carcinoma. Neth J Med 2009;153:124-128.
7. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl.
8. Vasen H, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 2007;44:353-362.
9. Arditi C, et al. Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. Endosc 2009;41:200-208.
10. Cairns S, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-689.
11. Loader S, et al. Patient vs. physician as the target of educational outreach about screening for an inherited susceptibility to colorectal cancer. Genet Test 2002;6:281-290.
12. Ouwens M, et al. Implementation of integrated care for patients with cancer: a systematic review of interventions and effects. Int J Qual Health Care 2009;21:137–144.
13. Trevena L, et al. A systematic review on communicating with patients about evidence. J Eval Clin Pract 2006;12:13-23.
14. Yoon P, et al. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. Prev Chron Dis 2009;6:A33.
15. Gagnon M, et al. Systematic Review of Factors Influencing the Adoption of Information and Communication Technologies by Healthcare Professionals. J Med Syst 2012;36:241-277.
16. Tugwell P, et al. Effective Consumer Investigative Group. Knowledge Translation for Effective Consumers. Phys Ther 2007;87:1728-1738.
17. Elwyn G, et al. How to develop web-based decision support interventions for patients: a process map. Pat Educ Couns 2011;82:260-265.
18. Van Gemert-Pijnen J, et al. A holistic framework to improve the uptake and impact of e-health technologies. J Med Internet Res 2011;13:e111.
19. Paling J. Strategies to help patients understand risks. BMJ 2003;327:745-748.
20. Fagerlin A, et al. Helping patients decide: ten steps to better risk communication. J Natl Cancer Inst 2011;103:1-8.
21. Metcalfe A, et al. Cancer genetic predisposition: information needs of patients irrespective of risk level. Fam Cancer 2009;8:403-412.
22. Hadley D, et al. Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. Arch Inter Med 2003;163:573-582.

23. O'Connor A, et al. A decision aid for women considering hormone therapy after menopause: decision support framework and evaluation. Pat Educ Couns 1998;33:267-279.

24. Elwyn G, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. BMJ 2006;333:417.

25. O'Neill S, et al. Familial risk for common diseases in primary care: the Family Healthware Impact Trial. Am J Prev Med 2009;36:506-514.

26. Ubel P, et al. The inclusion of patient testimonials in decision aids: effects on treatment choices. Med Decis Making 2001;21:60-68.

27. O'Connor A, et al. A survey of the decision-making needs of Canadians faced with complex health decisions. Health Expect 2003;6:97-109.

28. Dekker N, et al. Improving calculation, interpretation and communication of familial colorectal cancer risk: protocol for a randomized controlled trial. Implement Sci 2010;5:6.

Chapter 6

Improving recognition and referral of patients with an increased familial risk of colorectal cancer: results from a randomised controlled trial

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Submitted for publication

ABSTRACT

Aims: Only 12-49% of individuals with an increased familial colorectal cancer (CRC) risk are referred for effective preventive measures. This study determined use of and experiences with web-based and paper tools and their effect on uptake of genetic counselling (high risk) and surveillance colonoscopies (moderate risk).

Methods: Eighteen hospitals participated in a clustered randomised controlled trial. Nine intervention hospitals received access to a website for patients and clinicians, patient brochures, and education and pocket cards for clinicians. Patients in nine control hospitals received usual care. Data were collected from questionnaires and medical records.

Results: Data were complete for 358/820 CRC patients (44%) and 50/137 clinicians (36%) at baseline, and for 392/862 patients (45%) and 47/137 clinicians (34%) at endpoint.
Uptake of genetic counselling by high-risk patients was equal in the intervention group and the control group: 33% at baseline versus 15% at endpoint (p=0.003). Uptake of surveillance colonoscopies by moderate-risk relatives did not change significantly (intervention group: 33% at baseline versus 19% at endpoint; control group: 36% at baseline versus 41% at endpoint).
In the intervention group, 94/140 patients (67%) and 25/72 clinicians (35%) visited the website; 34/140 patients (24%) read the brochure. Patients valued clinicians' information as most useful; clinicians preferred pocket cards and education.

Conclusion: We found no effect of our tools on referral for preventive measures. Although the tools were appreciated, patients preferred clinicians' advice regarding referral for preventive measures. It may therefore be useful to aim future interventions at healthcare professionals to improve familial cancer prevention.

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INTRODUCTION

Surveillance colonoscopies for individuals with an increased familial colorectal cancer (CRC) risk decrease this risk with up to 80%.[1-3] Recommendations on surveillance colonoscopies and genetic counselling are given in international guidelines.[4-8] However, only 12-49% of increased-risk individuals are referred for these preventive measures.[9-13]

In the Netherlands, a hereditary CRC guideline was developed in 2008.[4] Three risk categories with corresponding preventive measures are distinguished. Individuals with a high familial CRC risk (above 15%) are advised to attend genetic counselling. A clinical geneticist then provides testing for hereditary cancer syndromes like Lynch syndrome and surveillance recommendations for patients and their relatives. For moderate-risk individuals (familial risk 10-15%), surveillance colonoscopies are recommended every six years from age 45. For low-risk individuals (familial risk below 10%), genetic counselling and surveillance colonoscopies are not recommended.

The mere existence of guidelines does not mean that they are adhered to in practice. Generally, multiple barriers exist to guideline implementation.[14] During development of the hereditary CRC guideline, clinicians and patients expected that important implementation barriers would be clinicians' lack of knowledge of familial CRC risk interpretation (i.e. determination of preventive measures) and communication, and a lack of awareness among patients. As guideline implementation strategies are most effective when they tackle existing barriers, a tailored multi-faceted strategy was developed.[14,15]

We performed a clustered randomised controlled trial (c-RCT) evaluating the effect of the implementation strategy on referral for preventive measures. We aimed to increase referral adherence of increased-risk patients from 30% to 50%.[9,15] To understand which elements of the implementation strategy were most effective, patients' and clinicians' exposure to and experiences with these elements were assessed in a process evaluation.

METHODS

Study design and setting

The c-RCT was performed among CRC patients and their clinicians (gastroenterologists and surgeons) in eighteen Dutch community hospitals.[15,16] Hospitals were randomised using a computerized randomisation system after stratification according to size (<500, 500-700,

and >700 beds) and number of departments (gastroenterology, surgery, or both). The nature of the intervention prevented blinding.

Participants

Newly diagnosed patients with colorectal adenocarcinoma under age 70 between January 1st and July 31st, 2009 were selected by the hospitals and invited to participate in the baseline measurements. Between June 2010 and January 2011, all CRC patients diagnosed in the seven months following an introduction meeting for clinicians were invited for the endpoint measurements. Patients with known hereditary CRC were excluded. Patients received an information letter, signed by their clinician or local study coordinator, with an informed consent form. In the baseline measurements and the control group, a questionnaire was sent with the information letter 2-9 months after diagnosis. In the intervention group, patients were invited 2-3 months after diagnosis and asked to provide their e-mail address on the informed consent form to receive a login code for the website, followed by a questionnaire 2-3 months later. Non-responders received one reminder.

Interventions

In nine control hospitals, the study was briefly introduced after the baseline measurements. Other than this presentation, usual care was followed. In the nine intervention hospitals, the implementation strategy was introduced, consisting of a website for patients and clinicians, patient brochures, and education and referral cards for clinicians.

The website contained evidence-based information on familial CRC risk, risk calculators for CRC patients and clinicians, and a decision support intervention for high-risk patients, supporting them in deciding whether to be referred for genetic counselling. In pilot tests, CRC patients and clinicians found the website easy to use, understandable and helpful in determining which preventive measures were recommended, and in deciding whether to be referred for genetic counselling. Website access was restricted to users who were e-mailed login codes.

Patient brochures, containing information on familial CRC risk and corresponding preventive measures, were given to clinicians for distribution among all new CRC patients.

Clinician education consisted of a 30-minute presentation on familial CRC risk assessment and referral for preventive measures, given during routine clinical meetings. Pocket cards with referral criteria for genetic counselling and surveillance colonoscopies were handed out during this presentation.

Outcome measures

The main outcome measure was the percentage of CRC patients and/or first-degree relatives undergoing preventive measures in accordance with guidelines.[4] Additional

outcome measures of the effect evaluation were the percentage of patients with whom their familial risk and preventive measures were communicated and the effect on the expected barriers: clinicians' and patients' knowledge and patients' willingness to undergo preventive measures. For the process evaluation, exposure to and experiences with the implementation tools were studied.

Power calculation

As described elsewhere, sixty clinicians and 300 CRC patients were needed to detect a 20% difference (30-50%) between the intervention group and control group in uptake of preventive measures by increased-risk patients, with alpha=5% and ICC=0.15.[15]

Data collection

Participants' characteristics

Patients' clinical characteristics such as age and educational level were collected with questionnaires and medical records. Clinicians completed anonymous questionnaires with items about their characteristics before and after the study.

Effect evaluation

Familial CRC risk

To determine whether family history was taken, questionnaires and medical records were used. If positive for cancer, the number of affected relatives, cancer type, age at diagnosis and level of kinship were collected from medical records. To determine familial CRC risk and corresponding indications for preventive measures, personal and family history of cancer were combined with the results from microsatellite instability (MSI) analysis, a test performed to determine the presence of an increased risk for Lynch syndrome.[4,17]

Preventive measures

We recorded uptake of preventive measures and whether these were in accordance with guidelines.[4] For high-risk patients and their relatives, attendance of genetic counselling or an appointment within the next six months was collected from questionnaires and familial cancer clinics. For moderate-risk families, patients were asked in questionnaires whether their relatives had planned or undergone one or more colonoscopies. For low-risk individuals, explicit absence of preventive measures was recorded as being in accordance with guidelines. Surveillance colonoscopies for CRC patients were not included, since they undergo colonoscopies for 5 years after diagnosis and not yet eligible for surveillance for their familial risk.

Secondary outcome measures

Clinicians' objective knowledge was measured using seven clinical vignettes.[16] Clinicians assessed familial CRC risk and preventive measures for each vignette. Patients' and clinicians' subjective knowledge of familial CRC risk and preventive measures was measured by asking them to score how much they felt they knew about these subjects on a Visual Analogue Scale of 0-100 mm.

From medical records and patient questionnaires, communication of familial CRC risk and preventive measures by clinicians was assessed. Aspects of communication by patients with relatives about familial CRC risk were assessed with the Openness to Discuss Hereditary Cancer in the Family Scale.[18]

Willingness to undergo preventive measures was determined by asking whether patients would want to attend genetic counselling, or whether their relatives would want to undergo surveillance colonoscopies, if recommended by their clinician.

Process evaluation

Questionnaires, attendance lists and website records were used to assess patients' and clinicians' exposure to the implementation tools. Their experiences with these tools were collected from questionnaires, including reasons not to use the tools. Perceived effectiveness was determined with questions about the tools' effect on knowledge, participation in decision making, and reassurance. Patients were asked whether they had discussed the website and brochure with their clinician and/or relatives. Patients and clinicians were asked to rate the three most useful tools. Clinicians were asked whether they would use the tools with future patients.

Data analysis

Clinical characteristics and outcome measures in high/moderate/low categories were reported using descriptive statistics, and compared between the intervention group and control group and between the baseline and endpoint measurements using univariate and multivariate logistic regression, independent samples T-tests and Pearson Chi-square tests. Multilevel analyses were not performed for lack of interhospital variation. All analyses were performed with SPSS v16.0, with significance at $p<0.05$.

RESULTS

Participants

Questionnaires were completed by 537/820 patients (65%) at baseline and 573/862 patients (66%) at endpoint (figure 1). During medical record analysis, 100 and 97 patients met exclusion criteria, respectively. Formal familial CRC risks could not be determined in another 79 and 84 patients since their medical records lacked data on family history and MSI analysis. Clinical characteristics from the final cohort (358 at baseline and 392 at endpoint) are shown in table 1. Baseline and endpoint questionnaires were completed by 50 (36%) and 47 (34%) of 137 participating clinicians, respectively.

Effect evaluation

Familial CRC risk

Family history was taken in 99% of patients at baseline (n=353) and at endpoint (n=388). Familial CRC risk was increased in 97 patients (27%) at baseline and in 118 patients (30%) at endpoint (figure 1).[16]

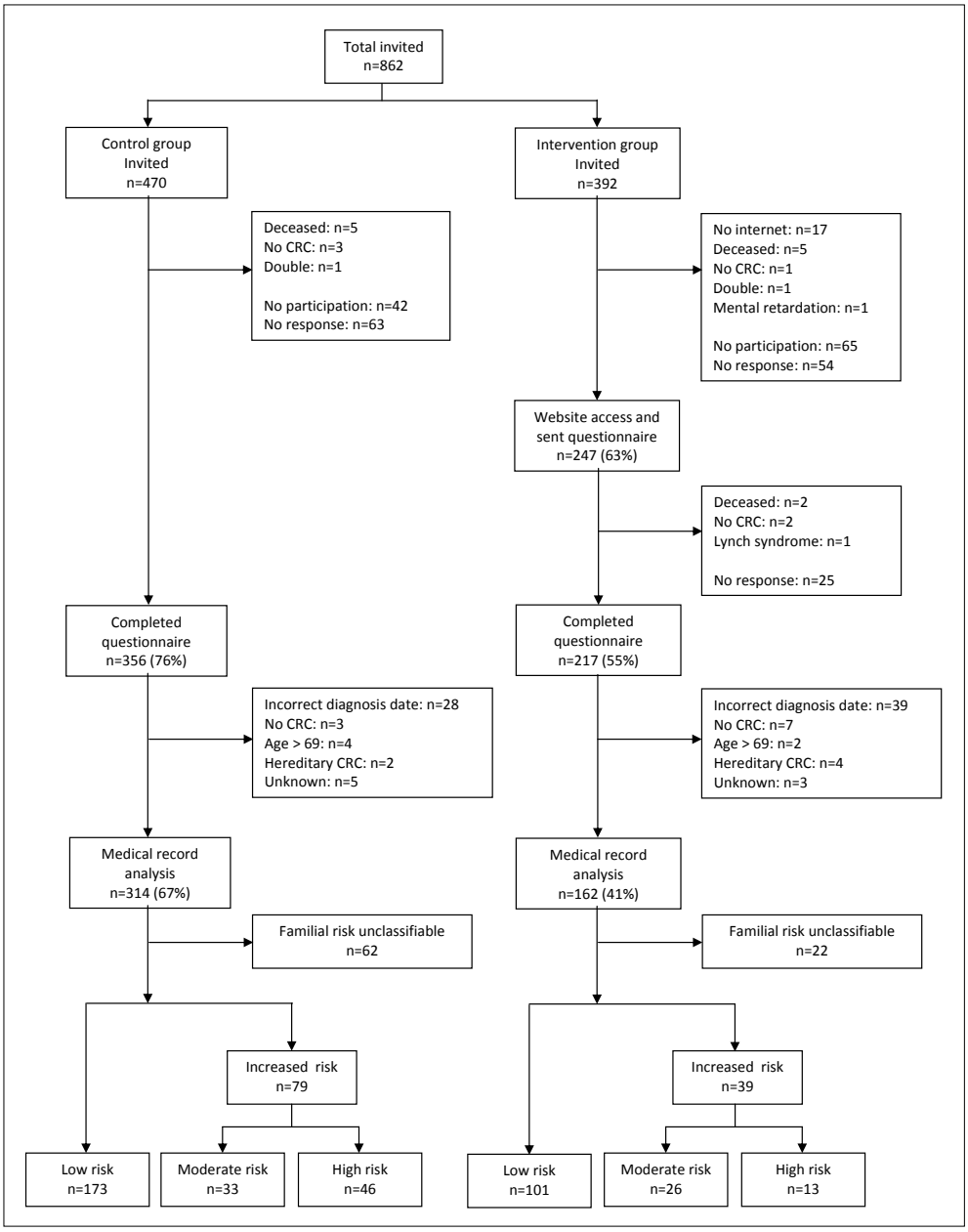
Table 1. Clinical characteristics of colorectal cancer patients

In table 1, clinical characteristics of the participating colorectal cancer patients are shown. Significant differences were seen for gender in the intervention group at baseline versus endpoint ([1] p=0.012); for TNM stage in the control group at baseline versus endpoint ([2] p=0.024); and for the distribution of familial risk of CRC at baseline in the intervention group versus the control group ([3] p=0.001). Totals do not always add up to 100% due to missing data and/or rounding off.

		Baseline				Endpoint			
		Intervention n=187		Control n=171		Intervention n=140		Control n=252	
		n	% / SD	n	% / SD	n	% / SD	n	% / SD
Gender [1]	Male	107	57%	109	64%	99	71%	167	66%
Age at diagnosis	Mean (SD)	59	7.6	60	8.2	60	7.3	59	7.5
Nationality	Dutch	185	99%	168	98%	136	97%	248	98%
Marital status	Married/cohabitant	152	81%	149	87%	116	83%	211	84%
Educational level									
	Low	60	32%	58	34%	33	24%	87	35%
	Medium	78	42%	72	42%	59	42%	98	39%
	High	48	26%	38	22%	44	31%	62	25%
Previous medical training		10	5%	9	5%	7	5%	16	6%
Personal history of cancer									
	Second CRC	8	4%	12	7%	7	5%	11	4%
	LSAT	1	1%	3	2%	2	1%	2	1%
TNM stage [2]									
	I	29	16%	29	17%	27	19%	62	25%
	II	53	28%	60	35%	38	27%	56	22%
	III	67	36%	62	36%	56	40%	100	40%
	IV	32	17%	17	10%	19	14%	32	13%
	Unknown	6	3%	3	2%	0	0%	2	1%
Tumour location (proximal)		42	23%	41	24%	39	28%	61	24%
Family history of cancer									
	CRC	54	29%	49	29%	44	31%	81	32%
	LSAT	9	5%	10	6%	8	6%	12	5%
Familial CRC risk [3]									
	High	9	5%	27	16%	13	9%	33	13%
	Moderate	39	21%	22	13%	26	19%	46	18%
	Low	139	74%	122	71%	101	72%	173	69%

CRC = colorectal cancer; LSAT = Lynch syndrome associated tumours (i.e. malignancies of the endometrium, ovaries, stomach, small bowel, bile ducts, upper urinary tract and sebaceous glands); SD = standard deviation; TNM = pathological staging of tumour size and invasion, lymph nodes and metastasis

Figure 1. Patient flow at endpoint



In figure 1, the flow of colorectal cancer patients in the endpoint group is depicted.
CRC = colorectal cancer

Preventive measures

Uptake of genetic counselling by high-risk CRC patients and their relatives was 33% at baseline versus 15% at endpoint (p=0.003), with equal percentages in the intervention group and the control group (table 2). Uptake of surveillance colonoscopies by moderate-risk relatives was comparable at baseline (intervention group: 33%; control group: 36%), but lower in the endpoint intervention group (19%) than in the control group (41%, p=0.015).

Secondary outcome measures

Overall, clinicians' knowledge was better in the intervention group than in the control group at baseline and endpoint (table 3). In the intervention group, knowledge of familial CRC risk was lower at endpoint compared to baseline (p<0.001), while knowledge of preventive measures had increased (p=0.010). In the control group, objective knowledge of familial risk (p=0.015) and preventive measures (p<0.001) was higher at endpoint, while subjective knowledge had decreased (p<0.001).

Patients' secondary outcomes are shown in table 4. Subjective knowledge of familial risk was higher in the endpoint intervention group than in the control group (p=0.024), while knowledge of surveillance colonoscopies was lower at endpoint compared to baseline in both the intervention (p<0.001) and the control group (p=0.035).

Familial CRC risk was communicated by clinicians with 23% of patients at baseline (n=84) and 37% of patients at endpoint (n=146; p<0.001), with increases in all risk categories, but no differences between control and intervention hospitals. In the endpoint intervention group, patients considered communication about familial CRC risk with relatives easier than at baseline (p=0.003) and compared to the endpoint control group (p=0.033).

Willingness to undergo preventive measures did not change after the intervention.

Table 2. Uptake of preventive measures by colorectal cancer patients

In table 2, the uptake of preventive measures is shown for colorectal cancer patients whose data from family history and microsatellite instability analysis were available for familial risk stratification. Significant differences were seen in uptake of surveillance colonoscopies between the endpoint intervention group versus the control group ([1]p=0.015).

	Baseline				Endpoint				Differences between baseline and endpoint	
	Intervention		Control		Intervention		Control		Intervention	Control
	n	%	n	%	n	%	n	%	*p*-value	*p*-value
Invited	374		446		392		470			
Included	187	50%	171	38%	140	36%	252	54%		
High familial CRC risk	9		27		13		33			
Genetic counselling	3	33%	9	33%	2	15%	5	15%	0.022	0.039
Moderate familial CRC risk	39		22		26		46			
Surveillance colonoscopies [1]	13	33%	8	36%	5	19%	19	41%	NS	NS
Low familial CRC risk	139		122		101		173			
Genetic counselling and/or surveillance colonoscopies	36	26%	25	20%	20	20%	38	22%	NS	NS

CRC = colorectal cancer; NS = not significant

Table 3. Objective and subjective knowledge in clinicians

In table 3, clinicians' objective and subjective knowledge scores are shown as a percentage. Significant differences were seen in objective knowledge between the intervention group and the control group at baseline ([1] $p<0.001$; [2] $p=0.005$) and at endpoint ([3] $p<0.001$; [4] $p=0.007$).

	Baseline		Endpoint		Differences between baseline and endpoint	
	Intervention n=25	Control n=25	Intervention n=20	Control n=27	Intervention	Control
	Mean	Mean	Mean	Mean	*p*-value	*p*-value
Objective knowledge of familial CRC risk						
High risk [1,3]	64	39	37	31	<0.001	0.004
Moderate risk [1,3]	57	37	22	33	NS	<0.001
Low risk [1,3]	65	50	82	78	NS	<0.001
Total [1,3]	61	40	48	44	<0.001	0.015
Objective knowledge of preventive measures						
High risk	63	61	66	64	NS	0.010
Moderate risk [1]	65	88	63	81	NS	<0.001
Low risk [1,3]	44	61	72	54	<0.001	<0.001
Total [2,4]	63	60	69	63	0.010	<0.001
Subjective knowledge						
Familial CRC risk	73	71	66	67	0.001	<0.001
Genetic counselling [3]	62	60	68	62	0.001	NS
Surveillance colonoscopies [3]	73	72	71	65	NS	<0.001

CRC = colorectal cancer; NS = not significant

Table 4. Secondary outcome measures in colorectal cancer patients

In table 4, the results of the secondary outcome measures among colorectal cancer patients at baseline and endpoint are shown. The possible range on all answers was 0-100, with higher scores reflecting better knowledge, more frequent or easier communication, and a higher need for support with communication. The bottom row shows the percentage of colorectal cancer patients willing to undergo preventive measures if recommended. Significant differences were seen between the intervention group and the control group in subjective knowledge at endpoint ([1]p=0.024); in ease of communication with relatives at endpoint ([2]p=0.033) and in willingness to attend genetic counselling at baseline ([3]p=0.037).

	Baseline		Endpoint		Differences between baseline and endpoint	
	Intervention n=187	Control n=171	Intervention n=140	Control n=252	Intervention	Control
	Mean / %	Mean / %	Mean / %	Mean / %	*p*-value	*p*-value
Subjective knowledge						
Familial CRC risk [1]	27	29	30	24	NS	NS
Genetic counselling	26	26	27	24	NS	NS
Surveillance colonoscopies	49	52	41	35	<0.001	0.035
Communication of familial CRC risk with clinician						
High familial CRC risk	22%	41%	46%	46%	NS	NS
Moderate familial CRC risk	50%	50%	54%	54%	NS	NS
Low familial CRC risk	15%	15%	38%	28%	0.001	0.001
Total	23%	22%	41%	35%	0.002	0.003
Communication of familial CRC risk with relatives						
Frequency	36%	38%	38%	34%	NS	NS
Ease [2]	56	59	65	59	0.003	NS
Need for support	21	19	27	26	NS	0.030
Willingness for preventive measures if recommended by clinician						
Genetic counselling (high-risk only) [3]	67%	85%	67%	76%	NS	NS
Surveillance colonoscopies (moderate-risk only)	69%	73%	62%	80%	NS	NS

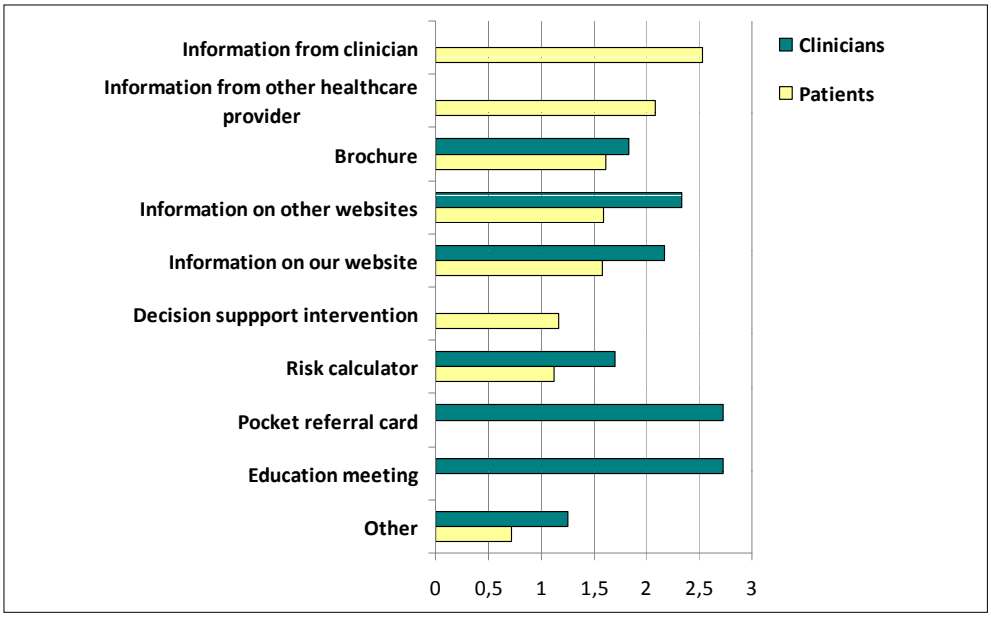
CRC = colorectal cancer; NS = not significant

Process evaluation

The website was used by 94/140 patients (67%), of whom 83 completed questionnaires. Sixty-one patients (73%) were positive about the website, mainly because it increased their knowledge (n=46), enabled them to better participate in decision making (n=29), and/or increased reassurance (n=25). Patients' main reasons not to use the website were not wanting to deal with potential hereditary CRC (n=40), and technical problems including forgotten login codes (n=34). Nine patients (11%) reported negative experiences, mainly increased worry (n=6) and/or confusion (n=6). Five patients (6%) discussed the website with their clinician or general practitioner, and 19 patients (23%) discussed it with relatives. Thirty-four patients (24%) read the brochure; 91% of patients who did not read it reported that they had not received it. Patients valued information from their doctor as the most useful, followed by the brochure and our website (figure 2).

Two-thirds of clinicians (n=48/72) attended the education meeting, and 25 (35%) used the website. Twenty clinicians completed questionnaires. They rated the referral cards and the education meeting as the most useful implementation tools (figure 2). Fifteen clinicians (75%) indicated that they intended to continue to use the tools.

Figure 2. Perceived usefulness of the implementation tools by patients and clinicians



In figure 2, the perceived usefulness of the implementation tools by colorectal cancer patients and clinicians is depicted. Higher scores reflect a higher perceived usefulness.

DISCUSSION

After introducing a tailored guideline implementation strategy, less individuals with an increased familial colorectal cancer risk attended surveillance colonoscopies and genetic counselling. CRC patients preferred advice from their doctor regarding preventive measures for an increased familial risk, while web-based and paper tools were appreciated as additional resources. Nevertheless, positive effects were seen regarding patient outcomes: familial risk was discussed more often, patients felt better informed and more able to participate in decision making, and found it easier to discuss familial risk and preventive measures with their relatives.

Unexpectedly, fewer patients underwent preventive measures at endpoint. Others have found that patients' uptake of CRC screening was lower after using a decision aid.[21] It is unlikely that this was the case in our study, since patients' willingness to undergo preventive measures did not change. Probably, less increased-risk patients were referred for preventive measures by their clinician. Clinicians may assume that patients do not want to be confronted with an increased familial risk shortly after receiving a cancer diagnosis, or referral may not have taken place yet, since referral was assessed 2-12 months after diagnosis.

Our findings are in line with an international survey among 15,165 people, where 88% of participants regarded clinicians as the most credible health information source.[19] Others found that the Internet was patients' first information source for hereditary cancer, followed by their doctor.[20] Since clinicians play such an important role, it is vital that they can identify and refer patients with an increased familial risk. Their knowledge needs to be improved, and clinicians realize this. It may be useful to focus on improving clinicians' familial CRC risk interpretation and communication, ensuring better referral, in addition to patients' understanding and acceptance of why they are (not) referred.

Our intervention was effective on improving patient-related outcomes. Patients who used the tools had better knowledge, felt they could participate better in decision making, and found it easier to communicate with their relatives. A strength of our study is the fact that the implementation tools were based on international evidence and developed together with potential users in a thorough manner, making the results applicable for non-Dutch patients and their clinicians. Furthermore, clinical practice was left undisturbed as much as possible, making it easier to estimate the effect of the implementation tools outside the research setting. However, only a limited number of participants used the implementation tools. Another limitation of this study is that using a combined intervention does not allow insight in what is more effective: clinician-directed or patient-directed components. Also, the

small number of patients with an increased familial CRC risk and the different recruitment of the endpoint intervention group need to be taken into account. A recruitment bias cannot be excluded, as shown by the differences in clinicians' knowledge and in patients' gender and TNM stage.

For better referral rates, familial CRC risk interpretation needs to be incorporated into routine clinical practice. Possible solutions include making one well-trained healthcare provider responsible for familial risk interpretation in all new CRC patients, and providing them with tools to do this, possibly further augmented with reminders.[22] Recently, we developed a digital referral test for assessment of familial CRC risk and preventive measures, which has a high sensitivity and was found easy to use.[23]

In this era of e-health and patient-based interventions, CRC patients value their doctors' advice as most important when considering preventive measures for an increased familial risk. Web-based and paper tools may be used additionally, to improve patients' knowledge, communication and participation in decision making. Since only a minority of CRC patients and their relatives undergo effective cancer preventive measures, improvement is needed. While empowering patients remains important, focussing on improving healthcare providers' knowledge may be needed for better cancer prevention.

REFERENCES

1. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
2. Järvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
3. Stupart D, et al. Cancer risk in a cohort of subjects carrying a single mismatch repair gene mutation. Fam Cancer 2009;8:519-523.
4. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl.
5. Vasen H, et al. Familial colorectal cancer risk: ESMO Clinical Recommendations. Ann Oncol 2009;20:S4:51-53.
6. Arditi C, et al. Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. Endosc 2009;41:200-208.
7. Cairns S, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-689.
8. Winawer S, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterol 2003;124:544-560.
9. Overbeek L, et al. Most patients with colorectal tumors at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008;51:1249-1254.
10. Van Dijk D, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 2007;6:131-134.
11. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
12. Foo W, et al. Family history? The forgotten question in high-risk colorectal cancer patients. Colorectal Dis 2009;11:450-455.
13. Staal-Rosier P, et al. Inadequate referral for genetic evaluations of patients with colorectal carcinoma. Neth J Med 2009;153:124-128.
14. Grol R, et al. What drives change? Barriers to and incentives for achieving evidence-based practice. Med J Aust 2004;180:S57–S60.
15. Dekker N, et al. Improving calculation, interpretation and communication of familial colorectal cancer risk: protocol for a randomized controlled trial. Implement Sci 2010;5:6.
16. Dekker N, et al. Familial colorectal cancer risk assessment in patients needs further improvement for more cancer prevention in relatives. Colorectal Disease 2013; in press.
17. Kievit W, et al. Cost effectiveness of a new strategy to identify HNPCC patients. Gut 2005;54:97-102.
18. Mesters I, et al. Openness to discuss cancer in the nuclear family: scale, development, and validation. Psychosom Med 1997;59:269–279.
19. Edelman Health Barometer 2011. http://www.edelman.com/healthbarometer
20. Kelly K, et al. How can we reach them? Information seeking and preferences for a cancer family history campaign in underserved communities. J Health Commun 2009;14:573-589.
21. Smith S, et al. A decision aid to support informed choice about bowel cancer screening among adults with low education: randomised controlled trial. BMJ 2010;341:c5370.
22. Overbeek L, et al. Electronic reminders for pathologists promote recognition of patients at risk for Lynch syndrome: cluster-randomised controlled trial. Virchows Arch 2010;456:653-659.
23. Dekker N, et al. Easy-to-use online referral test detects most patients with a high familial colorectal cancer risk. Submitted 2013

Chapter 7

Easy-to-use online referral test detects most patients with a high familial risk of colorectal cancer

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Submitted for publication

ABSTRACT

Aims: Currently, only 12-30% of individuals with a high risk for Lynch syndrome, the most common hereditary colorectal cancer (CRC) syndrome, are referred for genetic counselling. We assessed sensitivity, usability and user experiences of a new online referral test aimed at improving referral of high-risk individuals for genetic counselling.

Methods: Sensitivity was assessed by entering pedigree data from high-risk individuals (i.e., Lynch syndrome mutation carriers) into the referral test to determine whether genetic counselling was recommended. For usability, we assessed non-medical staff members' ability to determine referral according to guidelines in seven fictive clinical cases using the referral test after minimal training. Real-life users answered questions about their experience with the referral test.

Results: Sensitivity of the referral test was 91% for mutation carriers with CRC (n=164) and 73% for all affected and non-affected mutation carriers (n=420). Non-medical staff members (n=20) determined referral according to guidelines in 84% of cases using the referral test. Ten percent of real-life users (n=256/2470) provided feedback about experiences; 71% of them reported that the referral test increased reassurance, certainty about their familial risk and/or certainty about referral.

Conclusion: The referral test has a high sensitivity in detecting individuals with a high risk of Lynch syndrome and is suitable for use in clinical practice. Widespread use of the referral test should improve cancer prevention in high-risk patients and their relatives.

INTRODUCTION

Individuals with an increased familial risk of colorectal cancer (CRC) can decrease their risk of developing CRC with up to 80% by undergoing surveillance colonoscopies.[1,2] Surveillance recommendations depend on the familial CRC risk level, which can be high, moderate or low.[3-5] For individuals with a high familial CRC risk of more than 15%, genetic counselling is recommended. Based on family history and DNA analysis, a clinical geneticist can diagnose the presence of hereditary CRC such as Lynch syndrome (Hereditary Nonpolyposis Colorectal Cancer or HNPCC). Lynch syndrome is caused by mutations in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2* and the *EPCAM* gene.[6] Mutation carriers have a very high lifetime risk of developing CRC and endometrial cancer of up to 80% and 71%, respectively, and increased risks of other Lynch syndrome associated tumours such as ovarian, urothelial, gastric, and other cancers.[6-11] The risk of these cancers varies for different gene mutations; for example, extracolonic cancers are more prevalent in *MSH2* mutation carriers, compared to *MLH1* and *MSH6.*[8-10]

For individuals with a high familial CRC risk, surveillance recommendations in international guidelines include biennial colonoscopies starting at age 25, gynaecological surveillance from age 30-35, and in selected families, surveillance for urothelial and gastric cancer.[3-5] For individuals with a moderate familial CRC risk of 10-15%, less stringent surveillance is advised with colonoscopies once every 6 years from age 45 without genetic counselling.[3] For individuals with a low familial risk (below 10%), participation in population screening programs is recommended.

Both patients affected with cancer and their healthy relatives with a high familial CRC risk can be referred for genetic counselling, although further genetic testing is preferably performed in affected relatives first. In the Netherlands, costs of genetic counselling and testing are fully covered by health insurance, which is compulsory for all citizens. However, many CRC patients and their relatives encounter difficulties when determining whether they are eligible for genetic counselling, since little information is available to them.[12] Many clinicians lack knowledge on calculation and interpretation of the familial CRC risk, as these tasks are new for most clinicians outside the field of genetics.[13] Consequently, at present only 12-30% of CRC patients and their relatives at high risk for Lynch syndrome are referred for genetic counselling and highly effective surveillance colonoscopies.[14-16]

To improve referral rates for genetic counselling, providing clinicians, patients and their relatives with information on their familial CRC risk can be effective.[17] Prior research has shown that web-based interventions offer several advantages over traditional media such

as printed materials, including easy wide-spread distribution and tailoring of surveillance recommendations to individual users at low cost. [18-20] Such applications are highly acceptable to both patients and clinicians, provided they come from a reliable source, and are effective and easy to use.[21,22] Providing users with personal advices on how to decrease health risks is one important reason why users keep using health-related websites.[19]

Therefore, a new online referral test was developed, which provides users with recommendations for genetic counselling (for a high familial CRC risk), surveillance colonoscopies (for a moderate familial CRC risk) or neither, based on their personal and family history of CRC and related tumours. Before this referral test is implemented in daily practice, it is important to assess sensitivity, specificity, usability and real users' experiences. In the first part of this paper, we focus on the sensitivity of the referral test for identifying individuals with a high familial CRC risk for whom genetic counselling is indicated. Unfortunately, the specificity of the referral test could not be determined, because a control group from the general population could not be assessed for ethical reasons. In addition, we determine test usability by assessing whether non-medical staff members can determine appropriate referral using the test after minimal training. This would enable them to complete the referral test together with patients, thus enhancing the effectiveness and quality of the consultation with the clinician or general practitioner. Finally, we assess real users' experiences to improve the referral test. Therefore, the aim of this study was to (1) assess sensitivity of the referral test for identifying individuals with a high familial CRC risk eligible for genetic counselling; and (2) determine its usability and user experiences.

METHODS

Development of the referral test

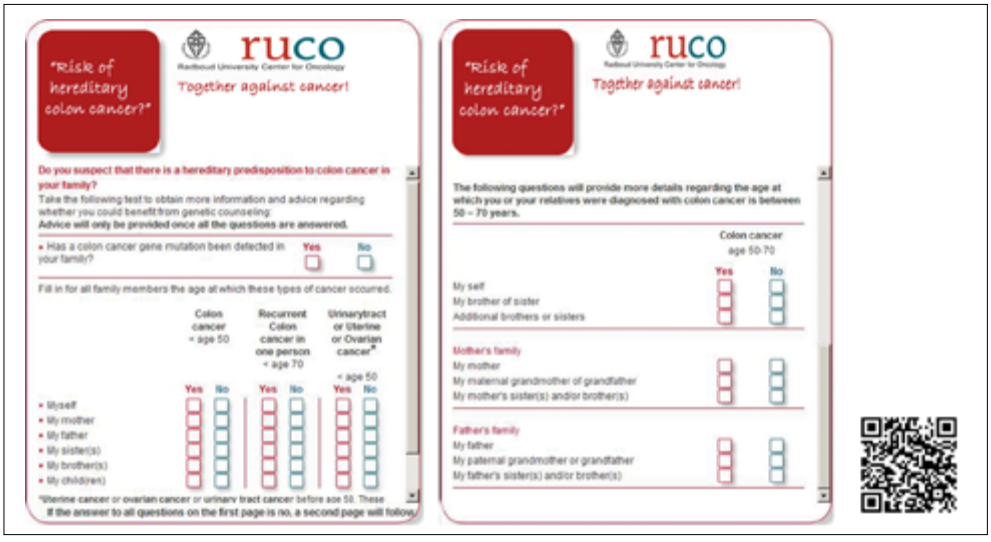
The aim of the online referral test "Risk of hereditary colon cancer" is to determine whether patients and their relatives are eligible for genetic counselling for a high familial CRC risk or surveillance colonoscopies for a moderate familial CRC risk. The version described in this article is aimed at healthcare providers as well as non-medical users from the general population, whether they are affected with CRC or not. The content was based on the Dutch guidelines on hereditary colorectal cancer.[3] A literature and an internet search were performed to identify existing risk calculation tools publicly available online, in English and/or Dutch. These tools were used as an inspiration for the format of our referral test. To check the quality of the results, the referral test was tested using scenarios representing all possible combinations of answers.

To assess acceptability, understandability and feasibility of completion, subsequent versions were reviewed by oncogeneticists and genetic counsellors, representatives from CRC patient organizations and non-medical personnel from the Radboud University Nijmegen Medical Centre (RUNMC). Changes were mainly textual. Opinions differed about the format of the answer options (filling in yes/no for each item versus only checking the applicable items); in the version of the referral test described in this paper, the yes/no option was used.

Format of the referral test

Users enter the history of CRC and other Lynch syndrome associated tumours such as endometrial, ovarian and urothelial cancer for patients and their first- and second-degree relatives (figure 1). These entries are weighed against the referral criteria for genetic counselling (for a high familial CRC risk) and surveillance colonoscopies (for a moderate familial risk) from the evidence-based guideline, as shown in table 1.[3] One of three possible results is provided: 1) high familial CRC risk with advice for genetic counselling; 2) moderate familial CRC risk with advice for surveillance colonoscopies every 6 years from age 45; or 3) low familial CRC risk with advice for no additional measures, as the Dutch population screening program had not yet started at the time of this study. Also, a link to more information is given. Non-medical users are recommended to discuss the results with their healthcare provider, who can then refer them for genetic counselling or surveillance colonoscopies in case of an increased familial CRC risk.

Figure 1. Screen shots and QR code of referral test



In figure 1, screen shots of the referral test are shown, which is freely available at http://www.umcn.nl/verwijzers (see QR code).

Sensitivity

First, the sensitivity of the referral test for genetic counselling was assessed. The referral test was completed by medical students for patients and their relatives with a high familial CRC risk (i.e., known Lynch syndrome mutation carriers), who had attended genetic counselling at the RUNMC familial cancer clinic between 1996 and 2011. All participants provided informed consent for pedigree use. Cancer diagnoses were confirmed through pathology reports. All pedigrees were entered into the referral test from the point of view of the index case, defined as the first patient or relative to have undergone DNA testing, and from the point of view of all relatives with an MMR gene mutation. Data for relatives were entered as if they were ignorant of the previous diagnosis of Lynch syndrome in their family. Whether or not the referral test recommended referral for genetic counselling was recorded. Fisher's Exact tests were used in SPSS v16.0 to compare sensitivity for different MMR gene mutations (*MLH1*, *MSH2*, *MSH6* and *PMS2*), level of kinship and cancer type (CRC, EC or other Lynch syndrome associated tumours). Significance levels were set at $p<0.05$.

Table 1. Set-up of the referral test

In table 1, the set-up of the referral test is shown. If individuals meet guideline criteria for a high familial risk of CRC, genetic counselling is recommended.[3] For those meeting criteria for a moderate familial risk of CRC but not a high familial risk, surveillance colonoscopies are recommended. No extra measures are recommended for individuals who do not meet criteria for an increased familial risk of CRC.

Question	Answer options	Referral advice
Colon cancer gene mutation in family	Yes	Genetic counselling
Colon cancer before age 50 in patient or first-degree relatives	Yes (one or more)	Genetic counselling
Recurrent colon cancer in one person before age 70 in patient or first-degree relatives	Yes (one or more)	Genetic counselling
Urinary tract, uterine or ovarian cancer before age 50 in patient or first-degree relatives	Yes (one or more)	Genetic counselling
Colon cancer between age 50-70 in patient, first-degree relatives or second-degree relatives	Three or more affected	Genetic counselling
	Two affected	Surveillance colonoscopies
	One or none affected	No extra measures
None of the above		No extra measures

Usability

If non-medical staff members such as a secretary complete the referral test together with the patient before the consultation, clinicians can use the saved time to discuss the actual referral. To determine whether non-medical staff members could assess referral in accordance with the guideline using the referral test, secretaries and other non-medical staff members from different RUNMC departments were invited to participate in a training to familiarise them with the referral test.[3] One of the study coordinators (ND) briefly introduced the referral test and asked participants to complete a random two out of seven fictive clinical cases (four high-risk, one moderate-risk and two low-risk cases). The referral test provided the referral advice (genetic counselling; surveillance colonoscopies; or neither), which the staff members reported back to the study coordinator. Three months later, the same staff members were asked to complete all seven cases by themselves (anonymously), and provided the referral advice that the test gave them.

We determined whether the referral advice was correct (i.e., in accordance with guidelines), underestimated (i.e., no referral advice for a moderate familial CRC risk, or no referral advice or surveillance colonoscopies for a high risk) or overestimated (referral advice for surveillance colonoscopies and/or genetic counselling for a low familial CRC risk, or genetic counselling for a moderate risk).[3] Baseline data (gender and age) and referral advices were reported using descriptive statistics from SPSS v16.0.

User experiences

For this study, the referral test was freely accessible for healthcare providers and non-medical users between January and May 2011. It was advertised to the general and medical press by the public relations department of the RUNMC and by employees of the department of Human Genetics during conferences, meetings etcetera.

Upon completion, all users were asked to provide anonymous feedback by answering four short questions about their experiences with the referral test. The first question concerned users' background: healthy relative with/without a family history of CRC, CRC patient, or healthcare provider. Next, we determined through what channel they had found the referral test (e.g., through the internet, recommendation from healthcare provider). Also, we asked how the referral test had helped them or not: by providing more or less certainty about users' familial CRC risk and surveillance options, and more or less reassurance. Finally, suggestions for improvement were collected.

RESULTS

Sensitivity

To determine whether the referral test would provide the correct result (i.e., high familial CRC risk with advice for genetic counselling), pedigree data from Lynch syndrome mutation carriers (n=420) were entered in the referral test. Eighty-three percent of the 81 index patients and 29% of the 339 relatives had CRC (table 2). Mismatch repair gene mutations were distributed as follows: 88 *MLH1*, 190 *MSH2*, 134 *MSH6* and 8 *PMS2* mutations.

Sensitivity varied between the different subgroups. The correct result "genetic counselling" was given for 90% of index patients and 73% of the total group. Sensitivity decreased from 83% in first-degree relatives to 60% in second-degree relatives (p<0.001). Healthy mutation carriers received advice for genetic counselling in 57% of cases, whereas affected mutation carriers received this advice in 91% if they had CRC (p<0.001) or endometrial cancer (p=0.002). No significant differences in sensitivity were found for the other Lynch syndrome associated tumours. The correct result "genetic counselling" was given more often in *MLH1* mutation carriers (85%) compared to those with *MSH2* (73%; p=0.03) or *MSH6* mutations (64%; p=0.001). All *PMS2* mutation carriers received advice for genetic counselling; this was not significant compared to the other MMR gene mutations.

Table 2. Lynch syndrome mutation carriers' baseline data and outcome of the referral test

In table 2, baseline data are shown from 420 Lynch syndrome mutation carriers whose pedigree data were entered into the referral test for the sensitivity analysis. In the bottom row, the number of individuals is shown for whom the referral test result was correct, i.e. "referral for genetic counselling for a high familial risk of CRC."

		Lynch – index n=81		Lynch – relative n=339		Total n=420	
		n	%	n	%	n	%
Gender	Male	39	48	169	50	208	50
Age [a]	Mean (standard deviation)	57	(12)	59	(22)	59	(20)
Cancer							
- None		1 [b]	1	202	60	203	48
- Colorectal cancer		67	83	97	29	164	39
- Endometrial cancer		11	14	10	3	21	5
- Lynch syndrome associated tumours [c]		1	1	14	4	15	4
- Other cancer		1	1	16	5	17	4
Outcome referral test: "High familial risk of colorectal cancer"		73	90	235	69	308	73

[a] Calculated by extracting the date of birth from the date of the study (March 31st, 2011)
[b] Patients with multiple colorectal polyps but no cancer
[c] Malignancies of the ovaries, stomach, upper urinary tract, small bowel and sebaceous glands

Usability

Twenty-six secretaries and other non-medical RUNMC staff members were invited to participate in a training session for the use of the online referral test. Six declined to participate for lack of time. Twenty of them (77%) completed one (n=2) or two cases (n=18). All were women; their median age was 43 years (range, 28-59 years). After completing the 38 cases, referral advice was in accordance with guidelines for 29 cases (76%) and overestimated in all remaining cases (24%).[3]

After three months, the same 26 non-medical staff members were asked to complete all seven cases. Again, 20 of them participated and completed all cases. Referral advice was in accordance with guidelines in 84% of cases, underestimated in 5% and overestimated in 11% (table 3).[3]

Table 3. Referral advice given by non-medical staff members using the referral test

In table 3, the referral advice given by 20 non-medical staff members using the referral test is shown for seven clinical cases. The answers in accordance with the guideline are shown in bold.[3]

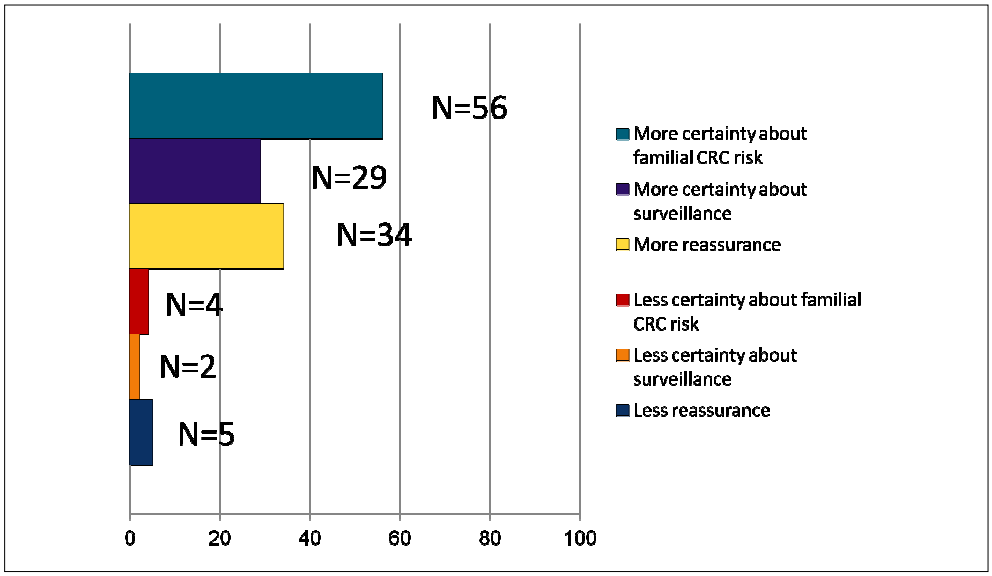
	Answer options	%
High familial risk of colorectal cancer (4 cases)	No results	5
	No extra measures (low risk)	8
	Surveillance colonoscopies (moderate risk)	0
	Genetic counselling (high risk)	**88**
Moderate familial risk of colorectal cancer (1 case)	No results	5
	No extra measures (low risk)	5
	Surveillance colonoscopies (moderate risk)	**60**
	Genetic counselling (high risk)	30
Low familial risk of colorectal cancer (2 cases)	No results	5
	No extra measures (low risk)	**75**
	Surveillance colonoscopies (moderate risk)	20
	Genetic counselling (high risk)	0

User experiences

In the four months that the referral test was freely accessible, it was completed 2470 times. The feedback questions were completed by 256 users (10%). Seventy percent were healthy individuals with a family history of CRC; 13% were healthy individuals without a family history of CRC; 13% were healthcare providers and 3% were CRC patients; 2% of the users did not answer this question. Sixty percent found the referral test through the internet, either through search engines or through direct referrals from other websites. Other sources (reported by 5-10% of users each) included medical societies, healthcare providers, medical journals, relatives and friends, and newspapers. In total, 181 users (71%) were positive

about the referral test. Details about their feedback are shown in figure 2. Eight users (3%) reported one or more negative effects: less certainty about their familial CRC risk (n=4) or surveillance options (n=2), or less reassurance (n=5). Suggestions for improvement were provided by 59 users. Most of them wanted to include more relatives and receive more information about the familial CRC risk.

Figure 2. Opinions of real-life users about the referral test



In figure 2, the opinions of real-life users about the referral test are depicted. Users could provide more than one answer.

DISCUSSION

This study supports the use of our online familial colorectal cancer referral test in clinical practice, as it reliably identifies those at high risk for Lynch syndrome, is easy to use, and has positive user experiences. Non-medical staff members in our study used the referral test correctly in 84% of cases after only minimal training.

As expected, sensitivity of the referral test was higher for mutation carriers affected with cancer than for healthy relatives. Also, referral for genetic counselling was recommended significantly more often by the test for *MLH1* mutation carriers compared to carriers of *MSH2*

and *MSH6* mutations. This is surprising, since *MLH1* and *MSH2* confer a similar CRC risk.[8] However, extracolonic cancers are more prevalent in *MSH2* mutation carriers, compared to *MLH1* and *MSH6*.[8-10] Since the referral test focuses on CRC, it will recognize those at high risk for Lynch syndrome less often in families with more extracolonic Lynch syndrome associated tumours. Since MMR gene mutations are found in only a small proportion of patients undergoing genetic testing, the actual sensitivity for untested individuals may be even higher.

Our referral test has several advantages over other available tools. Previously, two tools for patients were developed, aimed at collecting family history to determine their risk of hereditary CRC.[22] These tools facilitated professional nurses in selecting CRC patients eligible for genetic counselling, as did our referral test, which could easily be used by non-medical personnel. Unfortunately, the authors do not provide the sensitivity of their tools. Their tools were paper-based, limiting widespread use, and differed from ours in the type of tumours (our tool includes urothelial cancer, but not gastric cancer and colon polyps). We did not include colon polyps, as the vast majority of affected individuals will not know whether they had adenomas (which influence their CRC risk) or other types of polyps that do not increase their CRC risk. Furthermore, one of their tools also included third-degree relatives. We did not include these in our referral test, as in the Dutch guidelines only first-degree and second-degree relatives are taken into account for familial CRC risk assessment.[3] Also, our tool is aimed at identifying moderate-risk individuals eligible for surveillance colonoscopies, not only high-risk individuals eligible for genetic counselling.

Several tools are available to help clinicians determine whether genetic testing for Lynch syndrome is indicated for their patients. These include the Leiden or Wijnen model, Barnetson or MMRpredict, MMRpro, AIFEG and $PREMM_{1,2,6}$ models.[23-27] These models provide quantitative estimates of MMR gene mutation risks, which may be difficult to interpret by clinicians outside the field of genetics, as no clear cut-off levels for referral for genetic counselling and testing are defined, and thus sensitivity of these models varies. The advantage of our referral test is the clear surveillance advice. Moreover, previous models have only included *MLH1*, *MSH2*, and *MSH6*, whereas our study has also included *PMS2* gene mutation carriers. The referral test recommended genetic counselling for all *PMS2* gene mutation carriers, suggesting a high sensitivity for *PMS2*. While *PMS2* may have the lowest penetrance for CRC, this high sensitivity may be explained by the fact that all but one *PMS2* gene mutation carrier had CRC.[11] Evaluation in a larger sample of *PMS2* gene mutation carriers is needed for more reliable conclusions.

Using the referral test, non-medical staff members determined the correct referral advice in 84% of clinical cases. The incorrect results were spread among staff members and cases, making it unlikely that these were due to users' misunderstanding or systematic misclassification of cases. Having non-medical staff help patients use the referral test may increase the effectiveness of the clinician or general practitioner and might actually improve referral rates.

A limitation of this study is that we concentrated on non-polyposis CRC patients in the sensitivity analysis. For the evaluation of MMR gene mutation-positive relatives, their knowledge of a familial mutation was ignored. Normally, they would have been referred for genetic counselling based on this information. Instead of directly using input from the patients or their relatives, the sensitivity analysis was based on data collected by experienced genetic counsellors and confirmed from pathology reports. This is not expected to significantly affect the data, as the accuracy of a family history of CRC, the main tumour type for the referral test, is approximately 90% for first-degree relatives.[28] Polyposis patients have not been evaluated. Most of these patients develop CRC before age 50; thus, the referral test will give advice for referral for genetic counselling.[29]

As said, the specificity of the referral test could not be determined, because a control group from the general population could not be assessed for ethical reasons. Also, sensitivity was only determined for the result "genetic counselling", not for surveillance colonoscopies for a moderate familial CRC risk due to the difficulty of collecting such individuals. Other limitations include the fact that the anonymity of the usability test prevented the assessment of intra-user reproducibility and that reasons for not completing the training or final usability questionnaire were not collected.

The referral test's popularity (almost 2,500 users in the first four months) shows that many people are interested in finding out whether they are eligible for preventive measures for an increased familial CRC risk. Currently, the referral test is only available for healthcare providers due to ethico-legal reasons. A patient version is under development, which will be more rigorously tested for its effect on psychosocial outcomes and effectiveness on referral for preventive measures before it is introduced in clinical practice. In addition, several users indicated that they wanted more detailed information on their familial CRC risk level and surveillance measures itself, even though many users like to use a simple online test that tells them whether genetic counselling is appropriate for them. Therefore, more detailed web- and paper-based materials, aimed at both patients and clinicians, are being evaluated in a randomised controlled trial.[30]

In conclusion, the online referral test presented here has a high sensitivity in detecting individuals with a high familial colorectal cancer risk and is suitable for use in clinical practice. Sensitivity is highest for patients affected with cancer, and higher for families with CRC than families with predominantly extracolonic Lynch syndrome associated tumours. The referral test is a promising new initiative for clinicians and non-medical staff members, who can easily use it to identify individuals with an increased familial CRC risk. These increased-risk individuals can then choose to take appropriate surveillance measures. As such, widespread use of the referral test could lead to better cancer prevention.

REFERENCES

1. Järvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
2. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
3. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl.
4. American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing. Gastroenterol 2001;121:195-197.
5. Vasen H, et al. Familial colorectal cancer risk: ESMO clinical recommendations. Ann Oncol 2009;20:51-53.
6. Ligtenberg M, et al. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. Nat Genet 2009;41:112-117.
7. Aarnio M, et al. Cancer risks in mutation carriers of DNA-mismatch-repair genes. Int J Cancer 1999;81:214-218.
8. Bonadona V, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304-2310.
9. Van der Post R, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. Med Genet 2010;47:464-470.
10. Capelle L, et al. Risk and Epidemiological Time Trends of Gastric Cancer in Lynch Syndrome Carriers in The Netherlands. Gastroenterol 2010;138:487-492.
11. Senter L, et al. The clinical phenotype of Lynch syndrome due to germline PMS2 mutations. Gastroenterol 2008;135:419-428.
12. Metcalfe A, et al. Cancer genetic predisposition: information needs of patients irrespective of risk level. Fam Cancer 2009;8:403-412.
13. Dekker N, et al. Familial colorectal cancer risk assessment in patients needs further improvement for more cancer prevention in relatives. Colorectal Disease 2013; in press.
14. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
15. Overbeek L, et al. Most patients with colorectal tumors at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008;51:1249-1254.
16. Van Dijk D, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 2007;6:131-134.
17. Loader S, et al. Patient vs. physician as the target of educational outreach about screening for an inherited susceptibility to colorectal cancer. Genet Test 2002;6:281-290.
18. Webb T, et al. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. J Med Internet Res 2010;12:e4.
19. Schneider F, et al. Identifying Factors for Optimal Development of Health-Related Websites: A Delphi Study Among Experts and Potential Future Users. J Med Internet Res 2012;14:e18.
20. Yoon P, et al. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. Prev Chronic Dis 2009;6:A33.
21. Gagnon M, et al. Systematic Review of Factors Influencing the Adoption of Information and Communication Technologies by Healthcare Professionals. J Med Syst 2012;36:241-277.
22. Dudley-Brown S, et al. Hereditary Colorectal Cancer in the Gastroenterology Clinic. How Common Are At-Risk Patients and How Do We Find Them? Gastroenterol Nurs 2009;32:8-16.

23. Wijnen J, et al. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. New Engl J Med 1998;339:511-518.

24. Barnetson R, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006;354:2751-2763.

25. Chen S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 2006;296:1479-1487.

26. Marroni F, et al. A genetic model for determining MSH2 and MLH1 carrier probabilities based on family history and tumor microsatellite instability. Clin Genet 2006;69:254-262.

27. Kastrinos F, et al. The PREMM (1,2,6) model predicts risk of MLH1, MSH2 and MSH6 germline mutations based on cancer history . Gastroenterol 2011;140:73–81.

28. Sijmons R, et al. Accuracy of family history of cancer: clinical genetic implications. Eur J Hum Genet 2000;8:181-186.

29. Galiatsatos P, et al. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385-398.

30. Dekker N, et al. Improving calculation, interpretation and communication of familial colorectal cancer risk: Protocol for a randomized controlled trial. Implement Sci 2010;5:6.

Chapter 8

Focusing on patient needs and preferences may improve genetic counseling for colorectal cancer

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ABSTRACT

During cancer genetic counseling, different items which counselors consider important are discussed. However, relatively little empirical evidence exists regarding the needs and preferences of counselees. In this study needs and preferences were assessed from counselees with a personal and/or family history of colorectal cancer (CRC), who were referred for genetic counseling regarding CRC. They received a slightly modified version of the QUOTE-GENE^{ca} questionnaire prior to their first visit to the Hereditary Cancer Clinic. Response rate was 60% (48/80 participants). Counselees rated the importance of 45 items assessing their needs and preferences regarding the content and process of genetic counseling. Participants rated the items regarding discussion of information about their familial CRC risk (100%) and preventive options (98%) as important or very important. Fewer participants rated items concerning general information on genetics as important. Sensitive communication during counseling was considered very important by a large percentage of counselees. Generally, no major differences were seen between participants in relation to individual characteristics. Our data suggest that focusing on familial CRC risk and surveillance options, in combination with sensitive communication may lead to better satisfaction with genetic counseling.

INTRODUCTION

The lifetime risk of developing colorectal cancer (CRC) in Western society is approximately 5-6%.[1,2] The majority of these patients have sporadic CRC, while familial and hereditary cancers account for approximately 15 to 20% of all CRCs.[3-5] In these families, healthy relatives of CRC patients have an increased risk of developing CRC themselves, which may be prevented by surveillance colonoscopies.[6-7]

Familial CRC risk is generally divided into three groups, based on cumulative lifetime risks of developing CRC:[8]

- Average – familial CRC risk below 10%
- Moderate – familial CRC risk of 10-15%
- High – familial CRC risk above 15%

For patients with a high familial CRC risk, referral for genetic counseling is recommended. During genetic counseling, patients and their relatives receive information on the consequences and nature of hereditary CRC, the most common being Lynch syndrome. In a subset of families, genetic analysis for Lynch syndrome is performed by microsatellite instability (MSI) and/or DNA-testing. Based on these test results and the interpreted family history, a tailored surveillance plan is proposed by the clinical geneticist or genetic counselor. Regular surveillance by colonoscopy is crucial for individuals with an increased familial CRC risk, as it can reduce CRC-related morbidity and mortality up to 80%.[6-7]

Currently, most at-risk individuals for CRC have not had a surveillance colonoscopy.[9] Amongst other reasons, one underlying cause seems to be the inadequate recognition of individuals at risk for CRC. To improve this aspect of healthcare, a new Dutch guideline on familial and hereditary CRC was introduced in 2008, in which clinicians have new tasks in calculating, interpreting, and communicating familial CRC risk.[8] These tasks should lead to better recognition of individuals at an increased familial CRC risk, enabling them to undergo surveillance colonoscopies.

Family history, the basis of clinical indication, does not predict by itself whether an individual undergoes CRC surveillance or not.[10] Therefore, there must be other barriers for at-risk individuals to undergo surveillance. Some of these barriers might even be related to socio-demographic factors, such as age or education level.[11-12] However, several studies showed that recommendation for CRC screening by a healthcare provider is a significant predictor of timely screening for individuals at increased risk for CRC.[10,13] Interventions also seem to be most successful when recommendations are tailored to individuals or communities.[14] From

this perspective, tailoring genetic counseling to the needs and preferences of the counselee may lead to better understanding of the importance of CRC screening and thus increase surveillance uptake.

The traditional model for cancer genetic counseling focuses on the systematic discussion of cancer genetics, medical facts, risks of developing cancer, psychosocial consequences, and surveillance policy. This model is based on general key goals of genetic counseling regarding hereditary cancer as previously established by the counselors: (a) identifying individual needs and concerns of the counselee, (b) providing information on genes and chromosomes, (c) giving an individual risk assessment in the context of supportive interaction, and (d) discussing the pros and cons of genetic testing and drawing up a surveillance plan.[15] During counseling, careful attention must also be given to the patient's autonomy and ability to make well-informed decisions regarding testing and adoption of preventive strategies.[16-17]

Counselors' main goals of genetic counseling for hereditary CRC are well known; however, to our knowledge, the needs and preferences of counselees have scarcely been assessed. Previous studies investigated women's preferences for the genetic counseling aspects of providing cancer, gene, and risk information (information); giving advice about cancer surveillance (surveillance); preparing for genetic testing (preparation); and assistance with decision-making (direction). The researchers found that women who were offered *BRCA1/2* testing had the highest preference for getting information and lowest preference for direction.[18-19] Counselees may also need information about the genetic counseling procedure prior to a first counseling visit.[20]

Yet, in order to provide optimal tailoring of genetic counseling for hereditary CRC, further investigation of specific needs and preferences of the counselee and their relation to socio-demographic factors is required. Knowing what patients need and prefer enables the counselor to tailor information on a surveillance plan as much as possible. Such a personalized recommendation for CRC screening by a healthcare provider may increase the probability that those individuals at risk for CRC will undergo timely surveillance.

This exploratory pilot study was performed to answer the following research questions: 1) During genetic counseling, which counseling items and communication strategies are important to counselees suspected of hereditary CRC?; and 2) Are counselees' preferences related to their individual characteristics such as medical history, genetic counseling history, gender, and age?

METHODS

Participants

Counselees referred to the Hereditary Cancer Clinic of the Radboud University Nijmegen Medical Centre, the Netherlands, between May 2010 and July 2010 for genetic counseling on hereditary colorectal cancer (CRC) were eligible for this study. Inclusion criteria were (a) referral for genetic counseling for familial CRC or Lynch syndrome, and (b) age 18 years and above. Counselors included both clinical geneticists and genetic counselors. Due to ethical reasons, no data were collected from non-participants.

Procedures

To evaluate counselees' requirements concerning genetic counseling in case of hereditary cancer, an instrument called QUOTE-gene^{ca} was developed by Pieterse et al.[21] In the current study, counselees received a standard invitation to the Hereditary Cancer Clinic, as well as a pre-visit anonymous questionnaire based on QUOTE-gene^{ca}. Counselees were asked to return the questionnaire within one week. Clinical records were consulted to determine the medical status of the participant (affected or unaffected with CRC) and whether the counselee was the first in the family seeking genetic advice (index patient) or sought presymptomatic testing (in case of a known mutation in the family). Mutation carriers were offered surveillance by regular colonoscopies. Non-carriers (true negatives, being patients in whom a known family mutation is not found) were told that undergoing surveillance was unnecessary. If there was no known family mutation and no mutation was found in the patient, either no surveillance plan or a less intensive surveillance plan was drawn up according to national guidelines for familial CRC, based on family history.[8]

Questionnaire

The first part of the pre-visit questionnaire assessed gender, age, education level and nationality. The main part of the questionnaire was based on the QUOTE-gene^{ca} questionnaire, which in turn is derived from the QUOTE scale ('Quality of Care Through the Patients' Eyes').[21-22] The QUOTE-gene^{ca} questionnaire intends to measure needs and preferences in genetic counseling for hereditary cancer. This questionnaire has been shown to capture relevant issues of concern with a high internal consistency, and is associated with previously validated measures of coping style and distress.[21] Some items were rephrased, without changing the content of each item. For example, the item "my risk or the risk for my family" was split into two separate items: "my own risk" and "the risk for my family." Also, an item about "the option of additional support by a social worker" was added. As these are minor changes, we expect the psychometric properties of our questionnaire to be comparable to the original QUOTE-gene^{ca} questionnaire.

The questionnaire contained a list of cancer-specific items and a list of generic items. Cancer-specific items included "own risk of developing cancer," "determination and meaning of being a carrier of a cancer gene," "emotional aspects for counselee and family," and "heredity of cancer in general." Generic items included "procedural aspects of counseling," "sensitive communication," "emotional support," and "assessment of susceptibility to the disease." Counselees rated the importance of each item using a four-point, Likert-type scale (1 = not important, 2 = fairly important, 3 = important, 4 = extremely important). For data analysis, ratings 1 and 2 were merged to "(not or fairly) important" and ratings 3 and 4 to "(very) important."

Data analysis

The interrelations between patients' needs and preferences and their individual characteristics were compared using cross tabs and the Pearson Chi-square test. Individual characteristics used in the statistical analyses were: gender (men *versus* women), age (< 35 years *versus* 35-50 years *versus* > 50 years), medical status (affected with CRC *versus* unaffected with CRC), education (low *versus* middle *versus* high) and medical background (medical background *versus* no medical background). Education levels were subdivided into "low" (primary school), "middle" (junior and senior secondary vocational education), and "high" (higher vocational education and university education). All computations were done with the SPSS statistical package (release 16.0). Two-sided *p*-values below 0.05 were considered to be statistically significant.

RESULTS

Participants

Forty-eight of 80 counselees (60%) participated in this study. Table 1 shows the baseline characteristics of these 48 participants. There were 22 men (46%) and 26 women (54%). Their mean age upon completion of the questionnaire was 51.6 years (SD=11.3; range=19-72).

Table 1. Participant baseline characteristics (n=48)[a]

		n	%
Age (years)			
	Mean (SD)	51.6 (11.3)	
	Range	19-72	
Gender			
	Men	22	46
	Women	26	54
Kind of referral			
	First in family seeking advice (index)	40	83
	Presymptomatic	7	15
Personal medical history			
	Participant affected with CRC	15	31
	Participant unaffected with CRC	33	69
Education [b]			
	Low	25	31
	Middle	20	42
	High	12	25
Social status			
	Living together (cohabitant, married)	39	81
	Living alone (single, widowed, divorced)	9	19
Medical background			
	No	40	83
	Yes	7	15
Nationality			
	Dutch	46	96
	Other	2	4

[a] Sample sizes vary due to missing data; [b] Low = primary school; Middle = junior and senior secondary vocational education; High = higher vocational education and university education. CRC = colorectal cancer; SD = standard deviation.

Needs and preferences prior to the first visit

As shown in table 2, counselor provision of information about the counselee's own risk of developing (a second) CRC, as well as this risk for relatives, was rated as important by every participant (100%). Almost every participant wanted to know what to do if they had an increased risk of developing CRC (98%). Counselor explanation of emotional consequences for themselves and for their family were rated as (very) important by 70% and 81% of participants, respectively. Fewer participants considered the items about heredity of cancer in general as (very) important, e.g. the prevalence of cancer in the Netherlands (35%).

Table 2. Frequencies of counselees' ratings of cancer-specific needs and preferences as important or very important (n=48)[a]

During counseling, the counselor should explain…	**(Very) important**	
	n	**%**
How risks for myself and my family are computed	46	96
Own risk of developing cancer		
My risk of developing cancer (again)	48	100
What to do if I have an increased risk of cancer	46	98
What to do if I do not have an increased risk of cancer	36	77
Determination and meaning of being a carrier of a cancer gene		
Whether the cancer in my family is hereditary	45	94
Why I am / am not considered for further examination	44	94
What it means to be a carrier of a certain gene	43	90
Possibilities of DNA-testing	43	90
What it means to be a carrier of a cancer gene	43	90
Limitations of DNA-testing	41	85
The procedure of DNA-testing	39	81
Emotional aspects for counselee and family		
My family members' risk of developing cancer (again)	47	100
What it means not to be a carrier of a cancer gene	40	83
Emotional consequences for my family as a result of genetic counseling	38	81
The procedure of studying the family history	35	74
Emotional consequences for myself as a result of genetic counseling	33	70
Heredity of cancer in general		
How cancer is inherited in a family	41	85
How often cancer is hereditary	34	71
Background information (chromosomes, DNA, genes)	34	71
The prevalence of cancer in the Netherlands	17	35

[a] Sample sizes vary due to missing data

With regard to generic items of genetic counseling, all participants considered it (very) important that the counselor takes them seriously, listens carefully, gives enough time and attention, involves them in decisions that are made, and provides clear and understandable explanations (100%). These items represent sensitive communication during genetic counseling; every item in this category was rated as (very) important by all or almost every participant. Fewer participants considered discussion by the counselor of the option of additional support by a social worker (44%), communication with family members (60%), and talking about the emotional aspects of the diagnostic procedure (65%) as (very) important. These items represent emotional support during genetic counseling (see table 3).

Items involving cancer-specific topics

Unaffected participants were more likely to consider receiving information about the procedure of studying the family history (very) important compared to participants affected with cancer. In other words, a greater percentage of healthy participants wanted to know how a genetic risk assessment is made compared to affected patients (85% vs. 50%, respectively; p=0.025). As reported previously, receiving an explanation about their own risk of developing cancer or developing cancer again was rated as (very) important by all participants. Thus, no major differences due to participants' background variables were seen for this item. No other significant relationships were obtained for participant characteristics and their ratings of the cancer-specific questionnaire items.

Differences on generic items due to participants' individual characteristics

Sensitive communication was (very) important for almost all participants and was not significantly related to their individual characteristics. However, women more often than men rated the item 'the counselor is open to their wishes, values and opinions' as (very) important (100% vs. 77%, respectively; p=0.015). No other significant differences on general items were seen as a function of participants' individual characteristics.

Table 3. Frequencies of counselees' ratings of generic needs and preferences as important or very important (n=48)[a]

During counseling, the counselor should…	(Very) important	
	n	%
Provide me with clear and understandable explanations	48	100
Sensitive communication		
Take me seriously	48	100
Listen carefully	48	100
Give me enough time and attention	48	100
Involve me in the decisions that are made	48	100
Be skilled	47	98
Give advice	47	98
Give me the opportunity to ask questions	47	98
Be open to my wishes, values and my opinions	43	90
Procedural aspects of counseling		
Give medical information	46	96
Explain the procedure of genetic counseling	46	96
Be punctual with appointments	45	94
Inform me sufficiently about what to expect	44	92
Cooperate well with my other doctors, e.g. GP or specialist	44	92
Give the opportunity to ask questions at any time	44	92
Explain the roles of the providers	42	88
Tell me how much time the diagnostic procedure takes	32	67
Assessment of susceptibility to disease		
Tell me what the risk for my family is	46	96
Tell me what my risk is	44	94
Carry out a DNA-test on me or a family member	39	81
Analyze the family history	38	81
Emotional support		
Provide me (also) with written information	43	90
Reassure me	36	77
Show understanding and sympathy	36	75
Talk about the emotional aspects of the diagnostic procedure	31	65
Discuss communication with family members	28	60
Discuss the option of additional support by a social worker	21	44

[a] Sample sizes vary due to missing data. GP = general practitioner

DISCUSSION

Major findings

The results of this study show that the most prevalent information topics perceived as important by counselees prior to their first genetic counseling session are their familial colorectal cancer risk and surveillance options. Additionally, sensitive communication during genetic counseling is considered of extreme importance by counselees. Fewer counselees considered emotional aspects and general information on genetics as important. Ratings of the importance of needs and preferences generally did not differ significantly between the different socio-demographic groups.

The meaning and importance of these findings

Sensitive communication during counseling was considered very important as well by a large percentage of counselees. Especially, counselees consider it very important that the counselor takes him or her seriously, listens carefully, gives enough time and attention, and involves him or her in the decisions that are made. Evidently, the interaction between counselor and counselee is viewed as fundamental for successful counseling. This was also seen in a study by Veach et al, who published the results of a consensus meeting among genetic counselors and other healthcare professionals, in which they describe a reciprocal-engagement model of genetic counseling practice including goals and strategies that can be used during the genetic counseling process.[23]

Our results can be used to adapt future genetic counseling on hereditary CRC to the needs and preferences of the counselee. By better adapting the genetic counseling to the needs and preferences of the counselee, consultation time can be saved and used to explain important and complex issues instead, such as familial CRC risk and surveillance options for those who are at risk for CRC. The focus of genetic counseling must be on topics considered important and less on topics not considered essential by both counselor and counselee. By adapting genetic counseling to counselees' preferences, counseling may become more effective and more attention can be given to surveillance options for those who warrant surveillance.

Although generally no significant differences in needs and preferences were found in relation to counselees' socio-demographic characteristics, it is important to keep in mind that every counselee has specific needs and preferences based on other factors. Besides, this study showed that sensitive communication was considered very important by every counselee. Counselors should take into account what might explain observed trends in different needs and preferences. For example, presymptomatic counselees may consider emotional aspects

during genetic counseling more important than patients who are the first members of a family seeking advice on hereditary CRC. These so-called index patients may not always foresee possible outcomes. In addition, in this study, healthy participants were more likely to consider it important to understand the process of genetic risk assessment compared to affected participants. It is possible that participants with CRC consider risk assessment less important because they were affected already with CRC. Also, the present findings suggest women consider it more important than men that the counselor is open to their wishes, values, and opinions. One explanation could be that men have more interest in facts and medical information, while women consider communication itself more important. In consideration of these interpersonal differences, counselors always need to verify a counselee's personal background and adapt their counseling to their individual situation.

Relation of the findings to those of similar studies

The results of our study are partly in line with findings from other research. Peacock et al showed that women's preferences include information and surveillance advice.[18] Our study distinguishes between medical information (see table 3) and background information (see table 2) and shows that especially medical information is considered (very) important by 96% of the counselees. The need for background information on chromosomes, DNA, and genes is considered (very) important by 71% of the counselees.

Our results also concur with previous findings by Pieterse et al.[21] In their study, 200 new counselees, primarily counseled for breast and colon cancer, completed a QUOTE-gene^{ca} questionnaire prior to their first consultation. They found that the patients' preferences when interacting with the counselor were receiving information, risk and preventive strategies for oneself and/or family members and information about the procedure of genetic counseling. Less patients considered emotional support and discussing emotional aspects as very important beforehand. However, 91% of the counselees in that study were women. This leads to difficulties with extrapolation of these findings to genetic counseling for late-onset diseases that men and women seek more equally, such as CRC. Although the power of our study was limited, no major significant differences in needs and preferences between men and women were found. This indicates that this instrument can be meaningfully adapted to counselees for other types of late-onset hereditary cancers.

In another study by Pieterse et al, 130 counselees, referred mainly for breast or colon cancer, completed a questionnaire containing the QUOTE-gene^{ca} before their first appointment at a genetic clinic.[20] They showed that counselees had a stronger psychosocial focus than counselors, as counselees initiated the discussion of emotional consequences of DNA testing more often than their counselor, compared to other topics assessed. However, our

study shows that counselees seeking presymptomatic testing consider emotional aspects of genetic counseling more important than those who are the first in the family seeking genetic advice. Providing more information on the counseling content and procedure prior to their visit may prepare counselees for possible unforeseen consequences of genetic counseling. Furthermore, new counselees may be advised to prepare for the visit more thoroughly, allowing them to verbalize questions more frequently during consultation.[20,24]

Study limitations

The results of our study are based on a limited number of counselees from one country. In addition, 40% of the eligible participants did not enroll in this study, possibly limiting generalizability of the results. Since no data were collected for the non-participants, the possibility of an enrollment bias cannot be excluded. However, a strength of our study is that the group of participating counselees was very diverse, for instance in age, being affected with cancer or not, education, and gender. Another limitation to consider is that, by asking preselected questions, participants get an idea of possible items being addressed during genetic counseling. The fact that these items are proposed in the questionnaire, implies that they are at least important to someone else. This may be the reason that some participants were inclined to score all topics as (very) important, which may cause a social desirability bias. Also, a four point scale without a mid-point appears to push more respondents towards the positive end of the scale.[25] In addition, educational level may have influenced counselees' understanding of the questionnaire items. However, the percentage of low educated participants is normal compared to the general population and almost all questions were answered in which no differences were seen among counselees with different education levels, suggesting that this was not the case.

Practice implications and research recommendations

The results of our study may contribute to optimal adaptation of genetic counseling for hereditary colorectal cancer to counselees' needs. Focusing on familial CRC risk and surveillance options may lead to better satisfaction with genetic counseling and improved adherence to surveillance policies. However, it remains important for all counselors to keep in mind that every counselee has their own specific needs and preferences. Since there is great variability among counselees, using a questionnaire such as the QUOTE-gene^{ca} prior to the first genetic counseling session may help genetic counselors to determine which items to discuss with the counselee. However, it is necessary to explore the best content and format as well as assess the added value of this strategy. Additionally, larger studies are needed to determine whether indeed, very few differences in needs and preferences are present between counselees with different socio-demographics. It will also be necessary to explore whether patient satisfaction and surveillance uptake for colorectal cancer can indeed be improved in this manner.

REFERENCES

1. Jemal A, et al. Cancer statistics, 2009. CA Cancer J Clin 2009:59:225-249.
2. Netherlands Cancer Registry. http://www.iknl.nl.
3. De Jong A, et al. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64:367-370.
4. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
5. Lynch H, et al. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932.
6. Dove-Edwin I, et al. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history of colorectal cancer: 16 year, prospective, follow-up study. BMJ 2005;331:1047.
7. Jarvinen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterol 2000;118:829-834.
8. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl.
9. Longacre A, et al. Screening colonoscopy use among individuals at higher colorectal cancer risk. J Clin Gastroenterol 2006;40:490-496.
10. Griffith K, et al. Influence of family history and preventive health behaviors on colorectal cancer screening in African Americans. Cancer 2008;113:276-285.
11. Bleiker E, et al. Screening behavior of individuals at high risk for colorectal cancer. Gasteroenterol 2005;128:280-287.
12. Halbert C, et al. Colon cancer screening practices following genetic testing for hereditary nonpolyposis colon cancer (HNPCC) mutations. Arch Int Med 2004;164:1881-1887.
13. Lewis C, et al. Older adults‘ attitudes about continuing cancer screening later in life: a pilot study interviewing residents of two continuing care communities. BMC Geriat 2006;3:10.
14. Powe B, et al. A review of intervention studies that seek to increase colorectal cancer screening among African-Americans. Am J Health Prom 2010;25:92-99.
15. Lobb E, et al. How do geneticists and genetic counselors counsel women from high-risk breast cancer families? J Gen Couns 2001;10:393-405.
16. Robson M, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol 2010;28:893-901.
17. Lobb E, et al. Tailoring communication in consultations with women from high risk breast cancer families. Br J Cancer 2002;87:502-508.
18. Peacock S, et al. A discrete choice experiment of preferences for genetic counselling among Jewish women seeking cancer genetics services. Br J Cancer 2006;95:1448-1453.
19. Apicella C, et al. Determinants of preferences for genetic counselling in Jewish women. Fam Cancer 2005;5:159-167.
20. Pieterse A, et al. Communication in cancer genetic counselling: does it reflect counselees’ previsit needs and preferences? Br J Cancer 2005:92:1671-1678.
21. Pieterse A, et al. QUOTE-gene(ca): development of a counselee-centered instrument to measure needs and preferences in genetic counseling for hereditary cancer. Psychooncol 2005;14:361-375.
22. Sixma H, et al. Quality of care from the perspective of elderly people: the QUOTE-elderly instrument. Age Ageing 2010;29:173-178.
23. Veach P, et al. Coming full circle: a reciprocal-engagement model of genetic counseling practice. J Gen Couns 2007;16:713-728.

24. Albada A, et al. Use and evaluation of an individually tailored website for counselees prior to breast cancer genetic counseling. J Cancer Educ 2011;26:670-681

25. Worcester R, et al. A statistical examination of the relative precision of verbal scales. J Market Res Soc 1975;17:181-197.

Chapter 9

General discussion

With every end there comes a new beginning

(Tarzan)

GENERAL DISCUSSION

For effective cancer prevention, it is important that individuals with an increased familial colorectal cancer (CRC) risk are identified and referred for adequate preventive measures such as surveillance colonoscopies, and those without such familial risk are not. The increasing amount of evidence regarding the effectiveness of preventive measures has led to the development of a Dutch multidisciplinary guideline on hereditary CRC in 2008.[1] In line with international guidelines, the Dutch guideline clearly distinguishes three familial CRC risk categories (high, moderate and low), each with corresponding recommendations for preventive measures.[1-4] These recommendations are: genetic counselling for a high familial CRC risk; surveillance colonoscopies for a moderate risk; and population screening with faecal occult blood tests in case of a low familial CRC risk, which in the Netherlands will start in 2013.[5] Difficulties with guideline implementation in clinical practice were expected by the developers, because familial CRC risk assessment, interpretation and communication, which are essential for adequate risk identification and referral for preventive measures, are relatively new to many clinicians outside the field of genetics.

The RISCO study (risk of colorectal cancer) was undertaken to study whether identification and referral of these at-risk individuals could be improved by introducing a multifaceted guideline implementation strategy aimed at CRC patients and their clinicians (gastroenterologists and surgeons). The purpose of the RISCO study was two-fold: 1) to explore the current situation regarding familial CRC risk assessment, interpretation and communication; and 2) to determine the effectiveness and feasibility of two guideline implementation strategies regarding familial CRC risk assessment, interpretation and communication in a clustered randomised controlled trial (c-RCT).

To determine whether the introduction of the new guideline had improved referral rates for preventive measures from the previously reported 12-30%, a cross-sectional study was performed in eighteen Dutch community hospitals (figure 1).[6-13] Results are described in chapter 2. These data also served as the baseline measurements for the c-RCT described in the second part of this thesis (chapters 4 through 6). In chapters 3 and 7, alternatives for guideline implementation were explored, such as the population CRC screening program and a novel online referral test. Familial CRC risk communication in the clinical genetics setting was studied in chapter 8.

In this final chapter, the principal findings from the RISCO study are summarised, compared to existing literature, and discussed. We reflect on the methods used in this thesis and provide implications for clinical practice and future research.

Figure 1. Overview of the hospitals participating in the randomised controlled trial

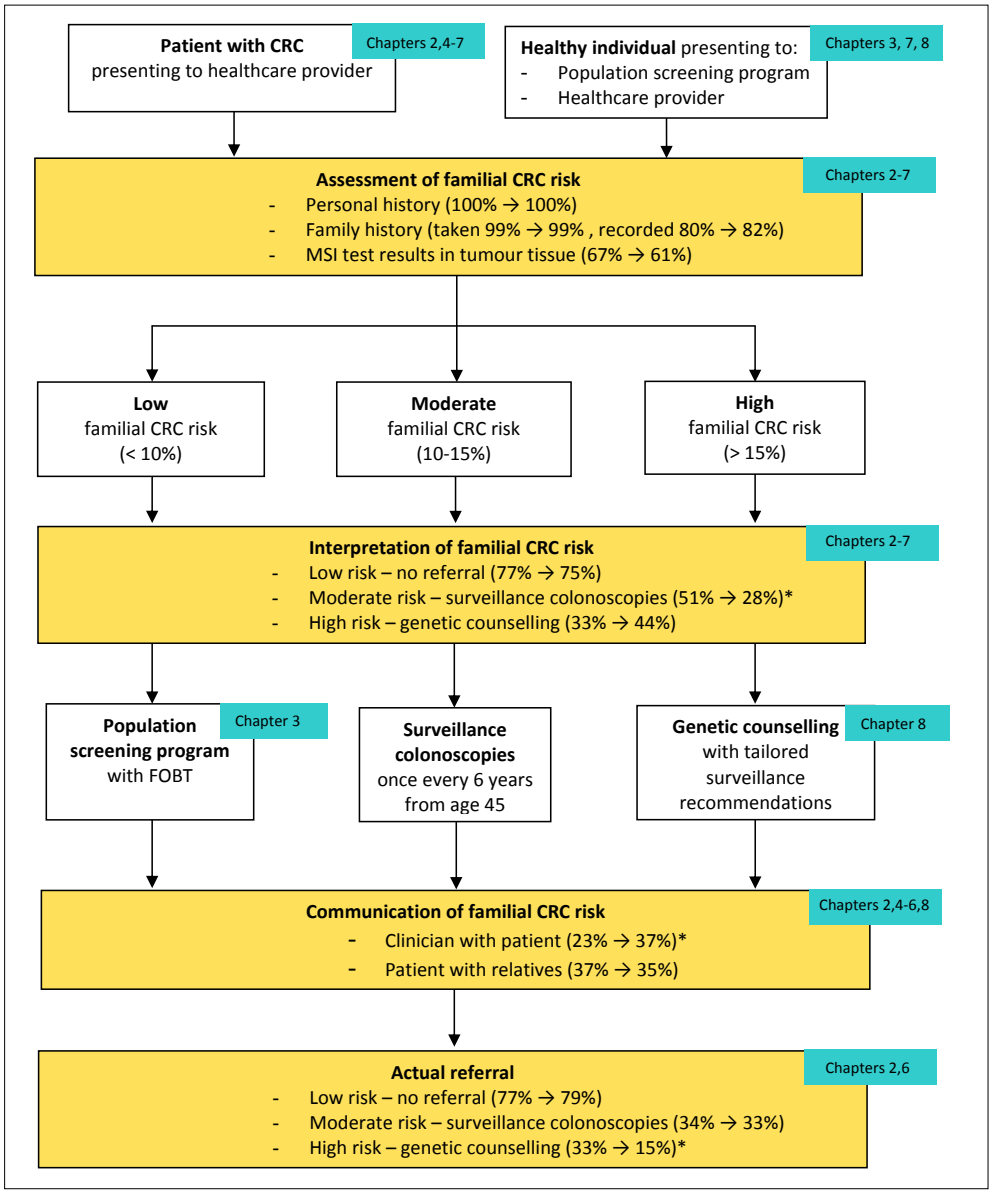
SUMMARY OF PRINCIPAL FINDINGS

The following principal findings can be formulated from the studies described in this thesis (figure 2):

- With traditional implementation methods, only one-third of colorectal cancer patients with an increased familial risk are referred for surveillance colonoscopies or genetic counselling in accordance with guidelines, while 23% of patients with a low familial risk is also referred for these preventive measures. *(Chapter 2)*
- Pilot tests of the RISCO website among patients and clinicians show that the website is easy to use, understandable, and is perceived as effective in improving knowledge. *(Chapter 5)*
- After the introduction of an intensive guideline implementation strategy, including the RISCO website, fewer patients and relatives with an increased familial colorectal cancer risk underwent preventive measures (surveillance colonoscopies and genetic counselling), while referral rates for these preventive measures did not change among low-risk individuals. *(Chapter 6)*
- Many clinicians lack knowledge of familial colorectal cancer risk and preventive measures (surveillance colonoscopies and genetic counselling). *(Chapters 2 and 6)*
- Although colorectal cancer patients and clinicians appreciated web-based and paper tools aimed at improving familial colorectal cancer risk assessment, interpretation and communication, patients preferred clinicians' advice regarding referral for preventive measures. *(Chapter 6)*
- Family history is taken in virtually all colorectal cancer patients, but reported in 82% of their medical records. *(Chapters 2 and 6)*
- Microsatellite instability analysis was performed in 63% of colorectal cancer patients meeting criteria for this analysis; and while most patients with a microsatellite instable tumour are referred for genetic counselling, most relatives of patients with microsatellite stable tumours are not referred for surveillance colonoscopies although these are indicated. *(Chapters 2 and 6)*
- After the introduction of an intensive guideline implementation strategy, clinicians discussed familial risk significantly more often with their patients (37% versus 23%). *(Chapters 2 and 6)*
- Six percent of participants with a positive faecal occult blood test in a pilot population screening program have an increased familial colorectal cancer risk. *(Chapter 3)*
- Performing familial colorectal cancer risk assessment in all participants of the population screening program could prevent an additional 172-184 colorectal cancers annually. *(Chapter 3)*

- Evaluation of a new online referral test for hereditary colorectal cancer showed that it has a high sensitivity in detecting individuals with a high risk of Lynch syndrome and is suitable for use in clinical practice. *(Chapter 7)*
- Genetic counselling for colorectal cancer may be improved by focussing on familial risk and preventive measures, combined with sensitive communication, as these items are considered the most important by counselees. *(Chapter 8)*

Figure 2. Pathway for familial colorectal cancer identification and referral



In figure 1, the pathway for familial colorectal cancer identification and referral is shown for colorectal cancer patients and individuals unaffected with cancer. Results are shown as 'baseline' → 'endpoint' measurements of the RISCO study. Recommendations for preventive measures are in accordance with national guidelines.[3] Chapters of this thesis in which the items are addressed are shown.
* $p<0.05$; CRC: colorectal cancer; FOBT: faecal occult blood test; MSI: microsatellite instability analysis

DISCUSSION OF PRINCIPAL FINDINGS

Referral for preventive measures

Principal findings regarding referral for preventive measures

With traditional implementation methods, only one-third of colorectal cancer patients with an increased familial risk are referred for surveillance colonoscopies or genetic counselling in accordance with guidelines, while 23% of patients with a low familial risk is also referred for these preventive measures. *(Chapter 2)*

After the introduction of an intensive guideline implementation strategy, fewer patients and relatives with an increased familial colorectal cancer risk underwent preventive measures (surveillance colonoscopies and genetic counselling), while referral rates for these preventive measures did not change among low-risk individuals. *(Chapter 6)*

After the introduction of an intensive guideline implementation strategy, clinicians discussed familial risk significantly more often with colorectal cancer patients (37% versus 23%). *(Chapters 2 and 6)*

In this thesis, we confirm existing data that less than half of CRC patients with an increased familial risk are referred for preventive measures in accordance with international guidelines, such as genetic counselling for a high familial CRC risk, and surveillance colonoscopies for a moderate familial risk, even after the introduction of an intensive guideline implementation strategy (chapters 2 and 6).[6-13] These low referral rates may be due to several reasons. In general, change is difficult, and the effect of implementation strategies is usually limited.[14] The hereditary CRC guidelines are complicated, and contain tasks in familial CRC risk assessment, interpretation and communication that are new to many clinicians outside the field of genetics.[1] Moreover, clinicians often lack time to take a complete family history, determine whether preventive measures are indicated, and communicate these with their patients.[15,16] This was also seen in our study, where even after the intervention, clinicians discussed familial risk with only 37% of colorectal cancer patients, versus 23% before this intervention (chapters 2 and 6). Similar percentages were seen in previous studies.[6]

Even though communication of familial CRC risk improved in all risk categories, referral rates for preventive measures did not. In fact, fewer patients underwent preventive measures after the introduction of the intensive implementation strategy. Patients' willingness to undergo preventive measures did not change before and after the intervention, suggesting that

fewer increased risk patients were referred for preventive measures by their clinician. Our finding supports this: more high risk patients reported receiving advice genetic counselling (44% versus 33% before) at the endpoint measurements (figure 1), although this difference was not statistically significant. However, referral advice for surveillance colonoscopies for relatives with a moderate familial CRC risk decreased significantly, from 51% to 28%. Referral may simply not have taken place yet, since referral data were collected 2-12 months after the intervention. A longer follow-up period may have shown higher referral rates but was not feasible in this study. Also, clinicians may assume that patients do not want to be confronted with an increased risk of CRC for their relatives shortly after receiving a cancer diagnosis. While family history is taken in most patients, subsequent assessment of whether preventive measures are indicated seems to be delayed often. Family history is usually taken during the first consultation, when the patient has just been diagnosed with cancer. Both patients and clinicians may consider it inappropriate to discuss a familial predisposition at this time, or during the subsequent treatment. However, many patients want to know as soon as possible whether their relatives (in particular their children) have an increased risk of developing cancer.[17] Landsbergen et al have shown that patients who were diagnosed with CRC less than one year before undergoing genetic analysis for Lynch syndrome, the most common hereditary CRC syndrome, reported less psychological distress than patients with a longer interval since diagnosis.[18] This supports guideline recommendations that familial CRC risk assessment needs to take place upon diagnosing CRC, because the risk of delaying referral is that it is often forgotten, thereby limiting the options of relatives with an increased cancer risk to take highly effective preventive measures.[1]

In addition to the under-referral of individuals with an increased familial CRC risk, almost one quarter of all CRC patients and their relatives with a low familial risk in our c-RCT were referred for surveillance colonoscopies and genetic counselling, which fall outside the indications of the current guideline.[1] We found that low risk individuals with a high educational level were referred for preventive measures more often than lower educated low risk patients (chapter 6). In addition, clinicians with less knowledge refer more CRC patients for unnecessary preventive measures. This over-referral has a significant impact. Besides increasing cancer-related worry in patients and their relatives, serious medical complications such as sustained bleeding or perforations occur in 0.1-0.3% of colonoscopies.[19-21] Furthermore, the costs of these referrals outside the current guideline are high, which is undesirable especially in the current climate of medical budget cuts.

Clinicians' knowledge of familial colorectal cancer risk and preventive measures

Principal findings regarding clinicians' knowledge of familial colorectal cancer risk and preventive measures

Many clinicians lack knowledge of familial colorectal cancer risk and preventive measures (surveillance colonoscopies and genetic counselling). *(Chapters 2 and 6)*

An important finding from our study is that unfortunately, many clinicians lack knowledge and skills in familial CRC risk assessment and referral for preventive measures (chapters 2 and 6). Clinicians' objective and subjective knowledge of preventive measures had improved after the intervention, even though no positive effect on referral rates was observed. It is likely that there is a delayed program effect, as the intervention should lead to short term and long term changes in referral behaviour, and behavioural changes generally take a long time.[22]

One option to improve correct referral rates would be to support healthcare providers with the risk calculators (chapter 5) or the online referral test (chapter 7) developed in this study. Both patients and clinicians were positive about the familial CRC risk calculator in the pilot tests and the c-RCT, and would recommend it to other patients and clinicians. Users of the referral test, including medical and non-medical personnel, found this referral test easy to use. However, implementation issues remain, as only 7 out of 72 clinicians in our study used the risk calculator (chapter 6). This may be due to lack of time or lack of internet access during the consultation. Also, clinicians may incorrectly assume that they already know whether or not to refer their patients. In our study, clinicians' subjective knowledge scores were higher than scores on clinical cases designed to assess their objective knowledge (chapters 2 and 6). Another explanation for the limited use of the risk calculator may be that clinicians are often sceptical of using web-based tools because they find that these tools do not work for them or the benefit of their patients.[23]

Patient awareness

Principal findings regarding patient awareness

Although colorectal cancer patients and clinicians appreciated web-based and paper tools aimed at improving familial colorectal cancer risk assessment, interpretation and communication, patients preferred clinicians' advice regarding referral for preventive measures. *(Chapter 6)*

Even in this era of e-health and patient-based interventions, CRC patients mainly rely on their doctors' advice when considering referral for preventive measures for an increased familial CRC risk (chapter 6). However, none of the implementation tools from the RISCO study influenced referrals by clinicians. This was also seen in a previous study to improve referral of colorectal cancer patients with a high familial CRC risk for genetic counselling, which was aimed at surgeons.[24]

Therefore, besides improving clinicians' knowledge and skills, it remains necessary to empower patients and their relatives, by making them more aware that they may have an increased familial CRC risk, and increasing their knowledge on the indications for preventive measures for them personally. A previous study has shown that patient-directed education is as effective in referral for genetic counselling as physician-directed education (42% vs. 51% referral, respectively).[25] Other options to improve patient awareness are discussed in the "Implications for clinical practice" section.

Identification of familial colorectal cancer risk

Principal findings regarding the identification of familial colorectal cancer risk

Family history is taken in virtually all colorectal cancer patients, but reported in 82% of their medical records. *(Chapters 2 and 6)*

Microsatellite instability analysis was performed in 63% of colorectal cancer patients meeting criteria for this analysis and while most patients with a microsatellite instable tumour are referred for genetic counselling as indicated, most relatives of patients with microsatellite stable tumours are not referred for surveillance colonoscopies although these are indicated. *(Chapters 2 and 6)*

Current guidelines recommend that family history be taken when a patient is diagnosed with CRC, and include cancer diagnoses of at least first- and second-degree relatives.[1,26-28] For all affected relatives, type of cancer, age at diagnosis, level of kinship and side of the family (maternal or paternal) need to be recorded. In our c-RCT, family history was reported in medical records in 82% of patients at both baseline (chapter 2) and endpoint measurements (chapter 6). Prior studies have shown a wide variation in this area, with entries of family history in medical records in 16-88% of cancer patients.[6-8,29-31]

The high family history assessment rates in our c-RCT do not automatically mean that the familial CRC risk based on the medical record data was always correct. Prior research has demonstrated that family history in medical records is not always complete and may lack information that is needed for familial risk assessment.[29-31] Missing data often include related tumours (such as endometrial cancer), age at diagnosis, and adequate information from relatives beyond the immediate family. This was also suspected in our study, but could not be confirmed as only family history for first-degree relatives was collected in the patient questionnaires.

Although family history is a useful tool for familial CRC risk assessment, it has its limitations. Families are getting smaller, restricting the informative value of a negative family history.[32] Additionally, patients are not always aware of their family history. Previous studies have shown that the accuracy of a family history for colorectal cancer in first-degree relatives is high, being approximately 90%.[15,33] Accuracy is lower for more distant relatives, and for extracolonic malignancies that influence familial CRC risk, especially gynaecological cancers which have a positive predictive value of 37-76% for first- and second-degree relatives. So while family history remains an important tool for the identification of familial risk, additional methods are needed to detect patients with an increased familial CRC risk without an obvious family history.

Besides family history, MSI analysis can be used for familial CRC risk assessment. This patient-directed approach has been shown to be complementary to family history by Manders et al.[34] In the Netherlands, MSI analysis can be initiated in recently diagnosed patients by the pathologist, when patients meet the so-called MIPA (MSI-analysis-by-a-pathologist) criteria.[35] These criteria include CRC before age 50, or a second CRC, or CRC and another Lynch syndrome associated tumour such as endometrial cancer before age 70. Other studies have shown a large variation in MSI analysis rates in patients meeting similar criteria, ranging from 14-59%.[24,36] In our c-RCT, MSI analysis was performed in 63% of CRC patients meeting MIPA criteria. This higher rate may be due to the reminder system for pathologists to perform MSI analysis in patients meeting MIPA criteria which was introduced in 2005-2006.[24] In an RCT, this reminder system was significantly associated with the identification of patients with a high familial CRC risk: 78% versus 59% of patients with or without the reminder system, respectively (OR 4.2 [95% CI 1.7–10.1]).

Another major finding of the RISCO study is that many clinicians need support in the interpretation of microsatellite instability (MSI) results. More than 90% of all CRCs associated with Lynch syndrome are MSI-positive, compared to 15% of sporadic CRCs.[37] Virtually all patients with an MSI-positive tumour in our study were referred for genetic counselling, in line with international recommendations.[1,37,38] In contrast, the majority of relatives of patients with an early onset MSI-negative CRC did not receive surveillance colonoscopies. If no other high risk criteria are met, these individuals are considered a moderate risk group, warranting surveillance colonoscopies once every 6 years from age 45.[1] Clinicians may assume that no further action is needed in case of an MSI-negative result. Also, in our experience, MSI results are usually reported later than the initial pathology report, in which case the clinician may miss them. More rapid ways to perform MSI analysis are worth looking into, especially since MSI status increasingly influences treatment decisions. Many studies have shown that patients with CRCs associated with Lynch syndrome do not benefit from 5-FU-based chemotherapy, while these patients may benefit from subtotal colectomy instead of limited resection to decrease their risk of metachronous CRCs, which may be as high as 29% within ten years.[39-42] A way to speed up the diagnosis of Lynch syndrome for surgical decision making could be to perform MSI analysis on the initial biopsy material, followed by a “fast-track” genetic counselling (i.e. genetic counselling after diagnosis but before the start of treatment) and testing for mismatch repair mutations. A pilot study in breast cancer patients has shown that such “fast-track” genetic counselling and testing may influence surgical treatment, without causing long-term psychosocial distress in the majority of patients.[43]

Implementation strategies

Principal findings regarding the implementation strategies

Pilot tests of the RISCO website among patients and clinicians show that the website is easy to use, understandable, and is perceived as effective in improving knowledge. *(Chapter 5)*

Although colorectal cancer patients and clinicians appreciated web-based and paper tools aimed at improving familial colorectal cancer risk assessment, interpretation and communication, patients preferred clinicians' advice regarding referral for preventive measures. *(Chapter 6)*

Evaluation of a new online referral test for hereditary colorectal cancer showed that it has a high sensitivity in detecting individuals with a high risk of Lynch syndrome and is suitable for use in clinical practice. *(Chapter 7)*

In chapter 5, the development and step-wise pilot testing of the RISCO website are described. One of the added values of our website over existing websites such as Family Healthware™ is that it combines information on familial CRC risk with risk calculators suitable for both patients and clinicians, and a decision support intervention for patients with a high familial CRC risk.[44,45] These pilot tests among CRC patients and clinicians showed that the website is easy to use, understandable and is perceived as effective in improving awareness and knowledge of familial CRC risk and preventive measures. Surrogate users also found that the decision support intervention helps patients in deciding whether to be referred for genetic counselling.

According to diffusion theory and social marketing principles, one of the main processes to increase the use of new web-based interventions is program development.[46,47] By considering and incorporating the opinions of potential future users, involvement is expected to increase, resulting in positive user experiences and higher levels of use.[48,49] New interventions should thus be developed in close collaboration with potential users from the target population. In our study, we confirmed how important it is to include representatives from all possible users in the development process of such tools. While both patients and clinicians offered important suggestions for improvements, their reasons to use the website and therefore their suggestions for adjustments differed significantly (chapter 5). Patients mainly wanted to use the website to obtain information and to review it at their own convenience. In contrast, clinicians mainly wanted to use the website to determine whether to refer their patients for surveillance colonoscopies and/or genetic counselling.

Since the tools on the RISCO website are quite extensive, and several users indicated that they would prefer a simpler tool to determine whether preventive measures are indicated for an increased familial CRC risk, an additional online referral test was developed (chapter 7). By completing the referral test for patients and their relatives with a high familial CRC risk (i.e. known Lynch syndrome mutation carriers), we showed that the referral test has a high sensitivity (91% for mutation carriers with CRC and 73% for all mutation carriers). Non-medical staff members in the study correctly identified preventive measures in 84% of seven clinical vignettes after only minimal training. If non-medical staff members complete the referral test together with patients before the consultation, clinicians or general clinicians can use the saved time to discuss the actual referral. This may actually improve referral rates in a cost-effective manner.

Even though colorectal cancer patients as well as clinicians were positive about the implementation tools, these tools proved not to be effective in improving referral rates for preventive measures (chapters 5 and 6). It is possible that the sample of patients and clinicians was not representative for the final users. Participating patients may have been more interested in using additional web-based and paper information. And although we did ask whether clinicians would use the tools, we did not go into depths about practical issues that may arise in real-life use. We cannot exclude the presence of a social desirability bias in the answers, as the pilot users reviewed the website and brochure in the presence of one of the researchers. Also, these tools were developed based on the barriers that were expected by guideline developers, namely clinicians' lack of knowledge and skills in familial CRC risk assessment, risk interpretation (i.e. determination of appropriate preventive measures) and risk communication, as well as a lack of awareness of the subject among CRC patients (chapter 1). Performing a more thorough analysis of possible barriers, as advocated by Grol, may have identified additional barriers which could have been tackled with other implementation strategies.[14] These may have included barriers on other levels, such as hospital or societal level, whereas we focussed on the patient and clinician level.

Population screening for colorectal cancer

Principal findings regarding population screening for colorectal cancer

Six percent of participants with a positive faecal occult blood test in a pilot population screening program have an increased familial colorectal cancer risk. *(Chapter 3)*

Performing familial colorectal cancer risk assessment in all participants of the population screening program could prevent an additional 172-184 colorectal cancers annually. *(Chapter 3)*

In the Netherlands, population screening will start in 2013 for individuals aged 55-75.[5] This screening program includes biennial immunochemical faecal occult blood testing (FOBT), followed by colonoscopy in case of a positive FOBT result. Screening is recommended for individuals with a low familial CRC risk only, since those with an increased familial CRC risk should be identified at a younger age, so they and their relatives can receive earlier, more intensive surveillance instead of FOBT.[5] With the current screening program, only participants with a positive FOBT are invited for colonoscopy and familial risk assessment. Thus, individuals with an increased familial CRC risk who decline to participate or have a negative FOBT will remain unidentified as being at-risk. In chapter 3, we show that 6% of participants with a positive FOBT have an increased familial CRC risk. Our findings are in line with international studies, which have shown that 4.2-4.9% of participants in a population screening have an increased familial CRC risk.[50,51] These prevalences are higher than previously reported in the general Dutch population, where 2.3% of unaffected participants reported a family history consistent with an increased familial CRC risk.[52] One possible explanation for this difference is that a positive family history of CRC is a reason to participate in a screening program.[53] Also, CRCs might occur more often in participants with an increased familial CRC risk compared to those with a negative family history.[54,55]

Adding familial CRC risk assessment to the new population screening program could prevent a significant number of CRCs compared to FOBT alone (chapter 3). We estimated that an additional 172-184 cases of CRC may be prevented annually among participants with a positive FOBT and their relatives in the eligible Dutch screening population of 3.5 million individuals (with an expected uptake of 60%).[5] This is just the tip of the iceberg, since many participants with a negative FOBT, as well as non-participants, also have an increased familial CRC risk.

Genetic counselling procedures

Principal findings regarding genetic counselling procedures

Genetic counselling for colorectal cancer may be improved by focussing on familial risk and preventive measures, combined with sensitive communication, as these items are considered the most important by counselees. *(Chapter 8)*

After high-risk CRC patients and their relatives have been identified and referred for genetic counselling, they are entitled to the best possible care at the familial cancer clinic. Familial CRC risk communication is a prominent part of the genetic counselling process. It is therefore important to identify the most effective risk communication strategies. Since involving patients in improving their own care is increasingly becoming standard practice, we assessed counselees' needs and preferences regarding the content and process of the genetic counselling session (chapter 8). Counselees (n=48) rated the importance of 45 items regarding their needs and preferences regarding the content and process of genetic counselling. This questionnaire was based on the QUOTE-Gene^{ca} questionnaire, which has been shown to capture relevant issues with a high internal consistency, and is associated with previously validated measures of coping style and distress.[56] Participants regarded information about their familial CRC risk (100%) and preventive measures (98%) as very important, as well as sensitive communication (100%). General information about heredity was rated as less important. This was also seen in another study, where information needs were also shown to be irrespective of risk level.[57] A systematic review has shown comparable results, namely that the supportive or emotional elements of genetic counselling provided more benefits to users than the informational or educational elements.[58]

These results suggest that focusing on familial CRC risk and preventive measures, combined with sensitive communication, may increase satisfaction with genetic counselling and result in more efficient counselling, as only topics that are important to the counselee and the counsellor are discussed. However, other authors have warned that a greater emphasis on the counselling and supportive elements of communication should be seen as complementary to the risk communication itself, as resolving or addressing emotional issues may help improve counselees' risk perception, responses to risk, and decision making.[58] Furthermore, using this approach may enhance adherence to preventive colonoscopies, since adherence increases when surveillance recommendations are tailored, and when their importance is clear to the counselee.[59]

METHODOLOGICAL REFLECTION

Strengths

A strong point of this thesis is the multidisciplinary approach. The starting point for the RISCO study was a multidisciplinary evidence-based guideline, which was developed by clinicians, researchers, patients and other experts to ensure that all aspects that are important for patient care were included in the guideline. This multidisciplinary approach was also followed in the knowledge measurements described in chapter 2, which were performed among all medical specialties involved in the care for CRC patients regarding hereditary CRC. This national study was undertaken to assess knowledge of familial CRC risk and preventive measures, which guideline developers considered to be one of the main barriers for guideline implementation.

Barriers for guideline implementation usually exist on different levels (e.g. organisational, clinician, and patient level).[14,60] Therefore, we evaluated a wide range of options to improve identification and referral of individuals with an increased familial CRC risk. This was done in different settings, as interventions are more likely to lead to changes in practice if they are aimed at multiple levels and focus on existing barriers in each target group.[14] In our study, we included not only hospital care (chapters 2 and 6), but also the population screening programme which will soon start in the Netherlands (chapter 3). In addition to the evaluation of referral for preventive measures, we studied how genetic counselling could be improved, by assessing counselees' needs and preferences regarding the content and process of the genetic counselling session (chapter 8).

Another strength of the research described in this thesis is the thorough development process of the implementation tools. Different innovative tools, such as the website used in the RISCO study (chapters 4-6) and the online referral test (chapter 7), were developed based on the Dutch guideline and a thorough search of other available literature, especially for risk communication (for the risk calculators) and shared decision making, including the criteria from the International Patient Decision Aids collaboration (for the decision support intervention).[1,61] The tools were then evaluated by patients and clinicians to create a solid basis for implementation (chapters 5 and 7). After pilot testing the RISCO implementation tools, their effectiveness and feasibility for improving familial CRC risk assessment, interpretation and communication were evaluated in a clustered randomised controlled trial (c-RCT). RCTs are generally considered to provide the highest level of evidence. Large numbers of patients from eighteen hospitals throughout the Netherlands completed questionnaires for the baseline measurements (n=537, 65% of invited patients, chapter 2) and the endpoint measurements (n=603, 70% of invited patients, chapter 6).

In any study, it is important to obtain the best possible view of actual practice to ensure reliability of the results. A good way to achieve this is by using mixed methods, which we did throughout our study. In the development process of the implementation tools and their evaluation in the c-RCT, a combination of qualitative and quantitative research was used (chapters 5 and 6). The risks of recall bias and social desirability bias were limited by adding the relatively objective data from medical records to patients' questionnaires. We found that clinicians discuss more with their patients than is reported in their medical records, something that was also seen in other studies.[62,63] Patient questionnaires were used to reveal these data, thereby further completing the picture of what really happened during the consultations.

In addition to evaluating the effectiveness of the implementation strategy as a whole, we gained insight in why the strategy did not improve referral rates for preventive measures as we had expected by looking at its feasibility. This was done by assessing actual use of the different elements of the implementation strategy by patients and clinicians, as well as their experiences with these elements in a process evaluation. Use of the implementation tools was limited, especially among clinicians. Patients appreciated the implementation tools, but only as an addition to the referral advice from their doctor, which was their main source of information and advice when deciding whether to be referred for preventive measures.

Limitations

An important limitation of the c-RCT is the high dropout rate after revision of the medical records, even though initial patient response rates were high (chapters 2 and 6). Hospitals provided lists of patients who were invited to participate. These lists were based on available hospital registries, which differed between hospitals, and included pathology reports but also clinical and financial registrations. In many cases, patients' date of diagnosis, determined from the initial pathology report, did not fall within the study period, leading to exclusion of the patient. Dropout rates were especially high in the endpoint intervention group. This may reflect a selection bias, even though we did not mention in the invitations that the study was about familial CRC risk to prevent the selection of patients with an increased familial risk, who may have been more interested to participate in such a study. Since it is known that many e-health technologies face adoption problems, it is also possible that patients did not want to participate because of the website, which was specifically mentioned in the invitation letter as participants were asked to provide an e-mail address for access to the website.[23]

While the total number of included patients was higher than needed according to the power calculations (300 patients), only 30% had an increased familial CRC risk (chapters 2 and 6). In addition to increasing the risk of a biased sample, which limits generalisability of the results, the small number of patients with an increased familial CRC risk prevented a detailed analysis of these subgroups. Future trials need to take this into account and base their power calculations on the expected number of patients with an increased familial CRC risk, even though this may affect feasibility due to the higher number of patients and hospitals necessary to perform a c-RCT.

The results of the studies among clinicians must be generalised with caution, since their response rates were low (chapters 2 and 6). Clinicians may be reluctant to complete questionnaires for research purposes while already experiencing a large workload.[64] This increases the risk of a selection bias, since the questionnaires may have been completed by motivated clinicians with a special interest in hereditary cancer. Also, the so-called Hawthorne effect may have influenced the results, as results from research tend to be better than results in actual clinical practice.[65]

Another limitation of the RISCO study concerns the limited use of the implementation tools, both among clinicians and patients, making the evaluation of their effectiveness difficult (chapter 6). The decision support intervention (DSI) was only used by 6/140 patients, all of whom had a moderate or low familial CRC risk and did not belong to the high-risk group for whom the DSI was intended. Systematic reviews have shown that DSIs can be cost-effective in improving patients' knowledge and improve agreement between patients' preferences and decisions regarding treatment, screening or surveillance.[66] In our study, patients may not have needed a DSI as they already knew whether they wanted to be referred for genetic counselling. Also, the sample may have been too small, as in this part of the study only 13 patients had a high familial CRC risk.

Finally, willingness and actual uptake of surveillance colonoscopies by relatives (chapters 2 and 6) were reported by the patient. Since these rates could not be confirmed for legal reasons, our results may not correctly reflect actual uptake.[67,68] It is known that relatives do not always inform each other that they had a colonoscopy.[69] The fact that surveillance recommendations for relatives were only recorded in medical records of a minority of patients suggest that most relatives were referred for surveillance colonoscopies by their own doctor.

IMPLICATIONS FOR CLINICAL PRACTICE

To improve the identification and referral of individuals with an increased familial colorectal cancer risk in clinical practice, two strategies are worthwhile focussing on: 1) increasing awareness of CRC patients and their relatives; and 2) supporting clinicians by increasing their knowledge in this area and improving the organisation of hospital care. In this section, we provide recommendations on how to achieve this. These recommendations are based on our own experiences, complemented with evidence from existing literature, and concern the entire referral process (figure 1).

Patient awareness

To improve the acceptance of familial CRC risk level and uptake of indicated preventive measures, it remains necessary to empower patients and their relatives by making them more aware that they may have an increased familial CRC risk and increasing their knowledge on the indications for preventive measures for them personally. They can then discuss this with their healthcare provider. In this process, effective information provision is essential, which could consist of a number of different strategies. For all these strategies, however, it is important to remember that health information materials for achieving patient involvement are most effective when they supplement or augment, rather than replace, interactions between patients and professionals.[66]

In a systematic review, it was shown that information provision using most available communication tools (websites, brochures etc.) is better than no communication tool for increasing knowledge about health issues.[70] Therefore, it may be useful to provide quality evidence-based information with tools that patients and their relatives can use to determine whether they are at risk and may benefit from preventive measures. In general, the effect of tools for communicating evidence on patient knowledge is larger if such tools are more structured, interactive and tailored.[58,70,71] The web-based and paper tools developed in the studies described in this thesis were highly appreciated by surrogate and real-life users (chapters 5-7). Making such tools publicly available through reliable sources could also improve knowledge and referral rates by enhancing patient awareness. Many patients are interested in obtaining cancer information and support online, and approve the use of computerized tools for familial risk assessment, particularly when provided to them by their clinician or healthcare organisation.[44]

It is then necessary to inform patients and their relatives of the existence of such tools, and to convince them of the importance of the information and the tools. This may be achieved with national media campaigns, either by starting new ones or by focussing existing cancer

campaigns on familial risk.[72] Such media campaigns can reach and possibly influence the general public as well as healthcare providers. In 2001, a mass media intervention consisting of newsletters and a week-long television series about hereditary cancer was launched in the New York region.[73] When performing telephone interviews with 254 random citizens, 80 reported having a conversation with their healthcare provider about hereditary cancer risks, of whom 9 received recommendations for genetic testing. A Cochrane review shows that mass media interventions may encourage the use of effective healthcare services, although another review found that their effect on guideline implementation is often limited.[66,72] Such campaigns should clearly describe both the characteristics of an increased familial CRC risk as well as a low familial risk to increase use of preventive measures among those with an increased familial CRC risk and limit such referrals in low risk groups. It has been shown that combined oral and written information can indeed reduce use of health service resources.[66]

In the Netherlands, population screening will start in 2013 for individuals with a low familial CRC risk aged 55-75.[5] The screening program includes biennial immunochemical faecal occult blood testing (FOBT), followed by colonoscopy in case of a positive FOBT result. This program may also have a beneficial effect on awareness of the general public, which has been shown to be low in a survey among the general public in 21 European countries in 2004.[74] A clear lack of awareness of family history as a risk factor for developing CRC was seen, with only 54% of 20,710 respondents being aware. Since this study was performed before the screening program and its pilots were introduced in the Netherlands, it is likely that awareness has increased since then.

Adding familial CRC risk assessment to the new population screening program could prevent a significant number of CRCs compared to faecal occult blood tests (FOBT) alone. In chapter 3, we show that an additional 172-184 cases of CRC could be prevented annually in the Netherlands with the current screening program. Following this strategy will miss participants with a negative FOBT, who form approximately 95% of the screening population.[75] We recommend that potential participants in this population screening program receive an invitation for familial CRC risk assessment along with the FOBT, to further enhance cancer prevention.

Clinician support

As patients become more informed about their familial CRC risk and preventive options, and more empowered to choose whether they want to make use of these measures, clinicians will need to respond effectively to this demand.[76] Overcoming the current knowledge gaps that are present among clinicians may be achieved by supporting them with easy and practical tools for familial CRC risk assessment and interpretation, such as the RISCO

website (chapters 4-6) and our novel online referral tool (chapter 7). The next challenge is to persuade clinicians to actually use these tools in clinical practice. Many clinicians use information and communication technologies in daily clinical practice, provided they are perceived as beneficial for the patient, and easy to use.[77] This is something that developers and implementers of such tools need to take into account, as well as existing barriers which often include lack of time and unfamiliarity with similar online tools. This latter barrier may improve with time, as web-based tools are increasingly being incorporated into clinical practice.

Clinicians realise that they lack knowledge, as shown by subjective knowledge scores of 60-73% even after the intervention (chapter 6). This state of "conscious incompetence" is an ideal basis for educational programs. Two-thirds of the clinicians attended the educational meeting. After the intervention, clinicians' objective and subjective knowledge scores increased slightly, but no effect on referral for preventive measures was seen. While knowledge has been shown to increase after single education sessions, a more structural training program, for instance a continuous e-based learning program, may have better results.[25,78] Such a program could become a standard item in the training of clinicians involved in the care for CRC patients, such as gastroenterologists, surgeons, oncologists and general practitioners, both in the education for medical specialists and general practitioners in training and as a part of the continuous training program for these healthcare professionals.

To support clinicians in identifying and referring more individuals with an increased familial CRC risk, the organisation of hospital care needs to be optimal. Much has already been achieved in our study and in previous projects, but further integration of familial CRC risk identification and referral for preventive measures in daily clinical practice is needed. One way to achieve this could be by making one healthcare professional responsible for familial risk assessment, interpretation and communication in all new CRC patients. A well-trained clinician or nurse practitioner could be appointed to do this. An Australian study has shown that dissemination of guidelines on surveillance colonoscopies among clinicians with supervision of all decisions by a nurse coordinator improved the proportion of surveillance decisions in accordance with guidelines for individuals with a moderate familial CRC risk from 62% to 96%.[79] Furthermore, discussing which preventive measures are indicated during multidisciplinary oncology meetings may serve as a constant reminder for all healthcare providers to collect their patients' family histories and MSI test results.

As said, most CRC patients with an MSI-negative tumour and their relatives are not recognised as having a moderate familial CRC risk and are not referred for surveillance colonoscopies. Perhaps this could be improved by changing the current pathology reports and state more

clearly that surveillance colonoscopies may be indicated for patients and relatives in case of MSI-negative results.[1]

Others have suggested that better referral rates of patients with an increased familial CRC risk may be achieved by performing MSI and/or immunohistochemical analysis (IHC) in all CRC patients, regardless of age at diagnosis and family history, followed by referral for genetic counselling if MSI/IHC results are suggestive of Lynch syndrome.[80-83] They showed that performing molecular analysis in all CRC patients detects 22-28% more patients with Lynch syndrome compared to using criteria which are based on age at diagnosis (such as the MIPA criteria) and family history (such as the Bethesda criteria).[38] Their results were further substantiated by cost-effectiveness studies, which have shown that universal testing has incremental cost-effectiveness ratios of $22,552- $88,700 per life year saved compared to age-dependent testing.[84,85] However, approximately 60% of MSI-high tumours in these studies were found to be sporadic. In contrast, the percentage of sporadic MSI-positive tumours was lower (47%) in patients meeting MIPA criteria.[34] In the Netherlands, testing for sporadic causes of MSI-positive tumours such as hypermethylation of the *MLH1* promotor is only performed after genetic counselling.[1] In the case of universal MSI analysis, this means that most patients who are referred for genetic counselling because of an MSI-positive CRC will not have a hereditary cancer syndrome. This will not only unnecessarily alarm patients and their relatives, but also increase the burden on the familial cancer clinic as well as costs. Applying the MIPA criteria for MSI analysis among newly diagnosed CRC patients has a cost effectiveness ratio of €2,184 per life year saved, which is substantially lower than in other studies.[35,84,85] We did not investigate whether simplifying the current criteria for MSI analysis improves the identification and referral of individuals with an increased familial CRC risk. However, based on the arguments presented here, we agree with current recommendations that only patients meeting MIPA and/or Bethesda criteria should undergo MSI analysis.[1,35,38]

IMPLICATIONS FOR FUTURE RESEARCH

Besides the recommendations in the preceding paragraphs, some additional ideas for future research are presented here.

First, to find out which elements may be particularly effective for future implementation strategies, more insight is needed on why the hereditary CRC guideline is implemented by some, and not by others. As research continues to find out why uptake of e-health technologies and implementation of guidelines in general are low, specific strategies can be developed that focus on relieving the relevant barriers.[14,23] Performing interviews or focus groups with clinicians could shed more light on how the hospitals with high correct referral rates achieve this, and what clinicians in hospitals with low correct referral rates need to improve these rates. And although our intervention did have positive effects on patient outcomes such as knowledge and communication, such effects on referral for preventive measures were not seen. Studying whether other strategies aimed at increasing patient and public awareness (see section "Implications for clinical practice") will be effective in improving referral rates could be a focus for future research.

A thorough cost evaluation could improve knowledge of the financial consequences of the current over- and under-referral of CRC patients and their relatives. In case of perfect referral, incremental costs per life year gained are estimated to be €980 when families with an increased CRC risk undergo surveillance, taking into account costs for all relatives referred to genetic counselling, including genetic risk assessment, mutation analysis, and surveillance colonoscopies (from age 25 and age 45 in case of a high and moderate familial CRC risk, respectively).[86] Another study has shown that applying the MIPA criteria for MSI analysis among newly diagnosed CRC patients is a feasible method to identify patients at risk for Lynch syndrome, with a cost effectiveness ratio of €2,184 per life year gained.[35]

FINAL CONSIDERATIONS

This thesis describes the current situation with regard to familial colorectal cancer risk identification and referral for preventive measures, as well as innovative interventions to improve referral rates. Even after the introduction of a multifaceted implementation strategy, less than half of CRC patients with an increased familial risk were referred for preventive measures in accordance with international guidelines, such as genetic counselling for a high familial CRC risk, and surveillance colonoscopies for a moderate familial risk. It is important to remember that guidelines are just that: tools guiding clinicians in their clinical decision making. Guidelines provide recommendations that may not be suitable for all patients, and therefore, 100% adherence to the guideline is not the ultimate goal of implementation trials such as ours. However, more attempts at improving guideline implementation remain necessary to further improve referral rates for preventive measures. We have shown that it may be useful to focus on clinicians to achieve this. In addition, we recommend that patients participate more actively in their own healthcare. Joint efforts of all stakeholders involved are needed to truly optimise the use of highly effective cancer prevention among colorectal cancer patients and their at-risk relatives.

REFERENCES

1. Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2008. http://www.oncoline.nl.
2. Arditi C, et al. Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. Endosc 2009;41:200-208.
3. Cairns S, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 2010;59:666-689.
4. Winawer S, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterol 2003;124:544-560.
5. Health Council of The Netherlands. A national colorectal cancer screening programme; 2009. Publication no.2009/13E.
6. Overbeek L, et al. Most patients with colorectal tumours at young age do not visit a cancer genetics clinic. Dis Colon Rectum 2008;51:1249-1254.
7. Van Dijk D, et al. Family history is neglected in the work-up of patients with colorectal cancer: a quality assessment using cancer registry data. Fam Cancer 2007;6:131–134.
8. Foo W, et al. Family history? The forgotten question in high-risk colorectal cancer patients. Colorectal Dis 2009;11:450–455.
9. Alberto V, et al. Family and personal history in colorectal cancer patients: what are we missing? Colorectal Dis 2006;8:612-614.
10. Staal-Rosier P, et al. Inadequate referral for genetic evaluations of patients with colorectal carcinoma. Neth J Med 2009;153:124-128.
11. Grover S, et al. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. Clin Gastroenterol Hepatol 2004;2:813-819.
12. Singh H, et al. Underdiagnosis of Lynch syndrome involves more than family history criteria. Clin Gastroenterol Hepatol 2010;8:523–529.
13. Wong C, et al. Value of database linkage: are patients at risk of familial colorectal cancer being referred for genetic counselling and testing? Int Med J 2008;38:328–333.
14. Grol R. Beliefs and evidence in changing clinical practice. BMJ 1997;315:418-421.
15. Sijmons R, et al. Accuracy of family history of cancer: clinical genetic implications. Eur J Hum Genet 2000;8:181–186.
16. Balogh E, et al. Patient-centered cancer treatment planning: improving the quality of oncology care. Summary of an Institute of Medicine workshop. Oncologist 2011;16:1800-1805.
17. Landsbergen K, et al. Genetic testing offered directly after the diagnosis of colorectal cancer: a pilot study on the reactions of patients. Genet Couns 2009;20:317-325.
18. Landsbergen K, et al. Shortened time interval between colorectal cancer diagnosis and risk testing for hereditary colorectal cancer is not related to higher psychological distress. Fam Cancer 2011;10:51-57.
19. Bokemeyer B, et al. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. Eur J Gastroenterol Hepatol 2009;21:650-655.
20. Regula J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006;355:1863-1872.
21. Ko C, et al. Serious complications within 30 days of screening and surveillance colonoscopy are uncommon. Clin Gastroenterol Hepatol 2010;8:166-173.
22. MacKinnon D, et al. Statistical analysis for identifying mediating variables in public health dentistry interventions. J Publ Health Dent 2011;71:S37-46.
23. Van Gemert-Pijnen J, et al. A holistic framework to improve the uptake and impact of eHealth technologies. J Med Internet Res 2011;13:e111.

24. Overbeek L, et al. Electronic reminders for pathologists promote recognition of patients at risk for Lynch syndrome: cluster-randomised controlled trial. Virchows Arch 2010;456:653-659.
25. Loader S, et al. Patient vs. physician as the target of educational outreach about screening for an inherited susceptibility to colorectal cancer. Genet Test 2002;6:281-290.
26. Lynch H, et al. Clinical impact of molecular genetic diagnosis, genetic counselling, and management of hereditary cancer: Part II. Hereditary nonpolyposis colorectal carcinomas as a model. Cancer 1999;86:1637-1643.
27. Severin M. Genetic susceptibility for specific cancers: Medical liability of the clinician. Cancer 1999;86:2564-2569.
28. Church J, et al. Practice parameters for the identification and testing of patients at risk for dominantly inherited colorectal cancer – supporting documentation. Dis Colon Rectum 2001;44:1404–1412.
29. Jenkins Vogel T, et al. A self-administered family history questionnaire improves identification of women who warrant referral to genetic counselling for hereditary cancer risk. Gyn Oncol 2012;125:693-698.
30. Lanceley A, et al. Family history and women with ovarian cancer: is it asked and does it matter? An observational study. Int J Gynecol Cancer 2012;22:254-259.
31. Sweet K, et al. Identification and referral of families at high risk for cancer susceptibility. J Clin Oncol 2002;20:528-537.
32. Yang Q, et al. Family history score as a predictor of breast cancer mortality: prospective data from the Cancer Prevention Study II, United States, 1982-1991. Am J Epidemiol 1998;147:652-659.
33. Ziogas A, et al. Validation of family history data in cancer family registries. Am J Prev Med 2003;24:190-198.
34. Manders P, et al. Young age and a positive family history of colorectal cancer are complementary selection criteria for the identification of Lynch syndrome. Eur J Cancer 2011;47:1407-1413.
35. Kievit W, et al. Cost effectiveness of a new strategy to identify HNPCC patients. Gut 2005;54:97-102.
36. Van Lier M, et al. Underutilization of microsatellite instability analysis in colorectal cancer patients at high risk for Lynch syndrome. Scand J Gastroenterol 2009;44:600-604.
37. Vasen H, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 2007;44:353-362.
38. Umar A, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268.
39. De Vos tot Nederveen Cappel W, et al. Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. Gut 2003;52:1752-1755.
40. Parry S, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut 2011;60:950-957.
41. Lindor N, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006;296:1507-1517.
42. Jover R, et al. The efficacy of adjuvant chemotherapy with 5-fluorouracil in colorectal cancer depends on the mismatch repair status. Eur J Cancer 2009;45:365-373.
43. Wevers M, et al. Breast cancer genetic counseling after diagnosis but before treatment: A pilot study on treatment consequences and psychological impact. Pat Educ Couns 2012;89:89-95.
44. Yoon P, et al. Developing Family Healthware, a family history screening tool to prevent common chronic diseases. Prev Chron Dis 2009;6:A33.
45. O'Neill S, et al. Familial risk for common diseases in primary care: the Family Healthware Impact Trial. Am J Prev Med 2009;36:506-514.
46. Rogers E. Diffusion of Innovations. New York, NY: Free Press; 2003.
47. Cugelman B, et al. Online interventions for social marketing health behavior change campaigns: a meta-analysis of psychological architectures and adherence factors. J Med Internet Res 2011;13:e17.

48. Schneider F, et al. Identifying factors for optimal development of health-related websites: a Delphi study among experts and potential future users. J Med Internet Res 2012;14:e18.

49. Crutzen R, et al. Bringing Loyalty to E-health: Theory Validation Using Three Internet-Delivered Interventions. J Med Internet Res 2011;13:e73.

50. Navarro M, et al. Colorectal cancer screening: strategies to select populations with moderate risk for disease. Rev Esp Enferm Dig 2009;101:855–860.

51. Worthley D, et al. Many participants in fecal occult blood test population screening have a higher-than-average risk for colorectal cancer. Eur J Gastroenterol Hepatol 2006;18:1079–1083.

52. De Jong A, et al. The frequency of a positive family history for colorectal cancer: a population-based study in the Netherlands. Neth J Med 2006;64:367–370.

53. Hlavaty T, et al. Positive family history promotes participation in colorectal cancer screening. Bratisl Lek Listy 2005;106:318–323.

54. Boutron M, et al. Family history of colorectal tumours and implications for the adenoma–carcinoma sequence: a case control study. Gut 1995;37:830–834.

55. Butterworth A, et al. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 2006;42:216–227.

56. Pieterse A, et al. QUOTE-gene(ca): development of a counselee-centered instrument to measure needs and preferences in genetic counseling for hereditary cancer. Psychooncol 2005;14:361–375.

57. Metcalfe A, et al. Cancer genetic predisposition: information needs of patients irrespective of risk level. Fam Cancer 2009;8:403–412.

58. Edwards A, et al. Personalised risk communication for informed decision making about entering screening programs. Cochr Datab Syst Rev 2003;1:CD001865.

59. Powe B, et al. A review of intervention studies that seek to increase colorectal cancer screening among African-Americans. Am J Health Prom 2010;25:92–99.

60. Grimshaw J, et al. Implementing clinical guidelines: current evidence and future implications. J Contin Educ Health Prof 2004;24(Suppl1):S31-S37.

61. Elwyn G, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. BMJ 2006;333:417.

62. Sikorskii A, et al. Concordance between patient reports of cancer-related symptoms and medical records documentation. J Pain Symptom Manage 2012;44:362-372.

63. Palaniappan L, et al. Population colorectal cancer screening estimates: comparing self-report to electronic health record data in California. Int J Canc Prev 2011;4:28540.

64. Rosemann T, et al. General practitioners' attitudes towards research in primary care: qualitative results of a cross sectional study. BMC Fam Pract 2004;5:31.

65. Mason J, et al. Designing evaluations of interventions to change professional practice. J Health Serv Res Policy 1999;4:106-111.

66. Coulter A, et al. Effectiveness of strategies for informing, educating, and involving patients. BMJ 2007;335:24-27.

67. Hoffmeister M, et al. Validity of self-reported endoscopies of the large bowel and implications for estimates of colorectal cancer risk. Am J Epidemiol 2007;166:130-136.

68. Bastani R, et al. Validation of self-reported colorectal cancer (CRC) screening in a study of ethnically diverse first-degree relatives of CRC cases. Cancer Epidemiol Biomarkers Prev 2008;17:791-798.

69. Jimenez J, et al. Physician-patient and patient-family communication after colonoscopy. Am J Gastroenterol 2012;107:1288-1295.

70. Trevena L, et al. A systematic review on communicating with patients about evidence. J Eval Clin Pract 2006;12:13-23.

71. O'Connor A, et al. Decision aids for people facing health treatment or screening decisions. Cochr Datab Syst Rev 2003;3:CD001431.

72. Grilli R, et al. Mass media interventions: effects on health services utilisation. Cochr Datab Syst Rev 2002;1:CD000389.

73. Piniewski-Bond J, et al. A cancer genetics education campaign: delivering parallel messages to clinicians and the public. J Cancer Educ 2003;18:95-99.

74. Keighley M, et al. Public awareness of risk factors and screening for colorectal cancer in Europe. Eur J Cancer Prev 2004;13:257-262.

75. Van Rossum L, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterol 2008;135:82–90.

76. Edwards A, et al. Interventions to improve risk communication in clinical genetics: systematic review. Patient Educ Couns 2008;71:4-25.

77. Gagnon M, et al. Systematic Review of Factors Influencing the Adoption of Information and Communication Technologies by Healthcare Professionals. J Med Syst 2010;36:241-277.

78. Schroy 3rd P, et al. A novel educational strategy to enhance internal medicine residents' familial colorectal cancer knowledge and risk assessment skills. Am J Gastroenterol 2005;100:677-684.

79. Bampton P, et al. Applying evidence-based guidelines improves use of colonoscopy resources in patients with a moderate risk of colorectal neoplasia. MJA 2002;176:155-157.

80. Recommendations from the EGAPP Working Group. Genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009;11:35–41.

81. Van Lier M, et al. Yield of routine molecular analyses in colorectal cancer patients ≤70 years to detect underlying Lynch syndrome. J Pathol 2012;226:764-774.

82. Hampel H, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783-5788.

83. Julié C, et al. Identification in daily practice of patients with Lynch syndrome (Hereditary Nonpolyposis Colorectal Cancer): Revised Bethesda guidelines-based approach versus molecular screening. Am J Gastroenterol 2008;103:2825–2835.

84. Ladabaum U, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2011;155:69-79.

85. Mvundura M, et al. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genet Med 2010:12:93–104.

86. Olsen K, et al. Cost-effectiveness of surveillance programs for families at high and moderate risk of hereditary non-polyposis colorectal cancer. Int J Technol Assess Health Care 2007;23:89-95.

Chapter 10

Summary / samenvatting

Less is more

SUMMARY

Approximately one quarter of all colorectal cancer (CRC) patients has an increased familial risk, meaning that their relatives have an increased risk of developing CRC themselves, which is at least twice as high as the population risk of 5-6%. It is important that these families are identified, so they can take highly effective preventive measures, including surveillance colonoscopies. However, prior research has shown that only 12-30% of individuals with an increased familial CRC risk is referred for genetic counselling or surveillance. This thesis contains the results of the RISCO study (risk of colorectal cancer) and additional studies, which were performed to improve the identification and referral of CRC patients and their relatives with an increased familial risk.

Chapter 1 is a general introduction, with information about the familial CRC risk and corresponding preventive measures. According to current guidelines on hereditary CRC, these are: genetic counselling for a high familial CRC risk (above 15%); surveillance colonoscopies once every 6 years starting at age 45 for a moderate familial CRC risk (10-15%); and no preventive measures for a low familial CRC risk (below 10%) other than participation in population screening with faecal occult blood tests (FOBT), which in the Netherlands will start in 2013. Furthermore, the rationale and goal of the studies in this thesis are described.

First, the current identification and referral of individuals with an increased familial CRC risk was studied in different settings. The first part of **chapter 2** contains a cross-sectional study which was performed in eighteen community hospitals to measure assessment and communication of familial CRC risk and referral for preventive measures in clinical practice, one year after the introduction of the new guidelines. CRC patients and their clinicians (gastroenterologists and surgeons) completed questionnaires, and medical records were analysed. This study also serves as the baseline measurements for the clustered randomised controlled trial described in chapters 4 and 6.
Familial CRC risk could be determined in 358/437 patients (82%). Of the 36 patients with a high familial CRC risk, 12 (33%) were referred for genetic counselling. Relatives of 21/61 patients with a moderate familial CRC risk (34%) underwent surveillance colonoscopies. Overall, 67% of patients with an increased familial CRC risk (n=65/97) and 23% of patients with a low familial CRC risk (n=61/261) were referred for preventive measures. Better referral of CRC patients and their relatives with an increased familial risk and less referrals for low-risk individuals are needed for better and more efficacious cancer prevention.

Doctors' knowledge plays an important role in the identification and referral of individuals with an increased familial CRC risk, and has been studied in the second part of **chapter 2**.

Gastroenterologists, surgeons and clinical geneticists from the Netherlands, including those in training, and general practitioners from the Nijmegen region (n=2,169) were sent a web-based questionnaire with ten clinical vignettes. For each vignette, a CRC patient with his/her family history was described. Participants provided familial CRC risk (high, moderate, or low) and preventive measures (genetic counselling, surveillance colonoscopies, or neither) for each vignette. Fourteen percent of doctors participated (n=312). They provided the correct familial CRC risk in 55% of the vignettes, and the correct preventive measures in 65% of vignettes. In conclusion, education of doctors is necessary and may lead to better cancer prevention.

In **chapter 3**, the prevalence of an increased familial CRC risk was assessed in participants in a pilot population screening program. In 324 participants with a positive FOBT, family history was taken by an experienced doctor or nurse. Six percent of these participants (n=17) had an increased familial CRC risk. If familial CRC risk is determined in all participants with a positive FOBT, and participants and their relatives with an increased familial risk are referred for surveillance colonoscopies and/or genetic counselling, an additional 172-184 CRCs could be prevented annually in the Netherlands.

Findings from the RISCO study and prior research demonstrate that many individuals with an increased familial CRC risk are not referred for preventive measures, leading to unnecessary morbidity and mortality. As such, there is still much room for improvement. In the second part of this thesis, the development and evaluation of improvement strategies are described, aimed at increasing the identification and referral of these at-risk individuals.

Chapter 4 contains a study protocol for a clustered randomised controlled trial (c-RCT). In nine of the eighteen hospitals described in chapter 2 (intervention group), a multifaceted implementation strategy was introduced, consisting of a website for CRC patients and clinicians, patient brochures, and education and pocket referral cards for clinicians. This was compared to usual care in nine control hospitals. In an effect evaluation, familial CRC risk assessment and communication and referral for preventive measures were determined. Actual exposure to and experience with the implementation strategy were assessed in a process evaluation.

The development and pilot test of the RISCO website is described in **chapter 5**. The website was developed together with clinicians, patients and researchers. It contains evidence-based information about familial CRC risk, risk calculators for CRC patients and clinicians to determine familial CRC risk and preventive measures, and a decision support intervention or decision aid, which supports CRC patients with a high familial risk in deciding whether

or not to be referred for genetic counselling. Twenty CRC patients and twelve clinicians participated in a pilot test of the website. Their suggestions for improvement mainly focussed on the navigation and the decision support intervention. After implementing these changes, patients and clinicians found the information understandable, and the website easy to use and helpful in deciding which preventive measures were indicated. Patients mostly considered the website useful for information, while clinicians mainly wanted to use it to determine whether or not to refer their patients for preventive measures.

Chapter 6 contains the results of the c-RCT. Data from the 358 CRC patients from the baseline group (see chapter 2) are compared to those from the endpoint group, where familial CRC risk could be determined in 82% (n=392/476). At baseline, one-third of patients with a high familial CRC risk (n=12/36) was referred for genetic counselling; surprisingly, this decreased to 15% at endpoint (n=7/46, p=0.003). No differences were seen between the intervention group and the control group. Uptake of surveillance colonoscopies by moderate-risk relatives was lower in the endpoint intervention group (19%, n=5/26) than in the control group (41%, n=19/46, p=0.015) and at baseline (intervention 33%, n=13/39; control 36%, n=8/22; p>0.05 for both groups).
Of the 140 patients in the intervention group, 94 (67%) used the website, and 34 (24%) read the brochure. Patients preferred advice from their doctor regarding preventive measures for an increased familial risk of CRC, while the website and brochure were appreciated as additional materials. Of the 72 clinicians, 25 (35%) used the website, and two-thirds (n=48) attended the education session. Clinicians rated the education and pocket referral cards as most useful. The low referral rates and limited use of the intervention materials suggest that further implementation strategies are needed.

Besides the tools that were studied in the c-RCT, a short online referral test was developed. In **chapter 7**, the sensitivity of the referral test for identifying individuals with a high familial CRC risk was determined. Data from 420 Lynch syndrome mutation carriers from 81 families were retrospectively entered into the referral test to determine whether genetic counselling was recommended. The sensitivity of the referral test was 91% for mutation carriers affected with CRC (n=164), and 73% overall. For usability, we assessed non-medical staff members' ability to correctly determine referral in seven clinical vignettes, using the referral test. Twenty participants provided the correct referral advice in 84% of cases after minimal training. Finally, 256/2470 real-life users (10%) answered questions about their experiences with the referral test. Seventy-one percent was positive about the referral test, since it provided them with more certainty about their familial CRC risk and/or preventive measures, and more reassurance.

Adherence to preventive measures increases when recommendations are tailored, and when their importance is understood. In the study described in **chapter 8**, questionnaires were sent to counselees referred for genetic counselling for an increased familial CRC risk, to determine how genetic counselling can be improved. Counselees rated the importance of 45 items assessing their needs and preferences regarding the content and process of genetic counselling. Participants (n=48) regarded information about their familial CRC risk (100%) and preventive measures (98%) as very important, as well as sensitive communication (100%). Focusing on these items may increase satisfaction with genetic counselling and improve adherence to surveillance colonoscopies.

In a general discussion in **chapter 9**, these findings are discussed, together with the limitations of the study, and the implications for patient care and research. Our overall conclusion is that even after the introduction of a multifaceted implementation strategy, less than half of CRC patients with an increased familial risk were referred for preventive measures in accordance with international guidelines, such as genetic counselling for a high familial CRC risk, and surveillance colonoscopies for a moderate familial risk. Therefore, more attempts at improving guideline implementation remain necessary to further improve referral rates for preventive measures. We have shown that it may be useful to focus on clinicians to achieve this. In addition, we recommend that patients participate more actively in their own healthcare. Joint efforts of all stakeholders involved are needed to truly optimise the use of highly effective cancer prevention among colorectal cancer patients and their at-risk relatives.

SAMENVATTING

Familieleden van ongeveer een kwart van alle patiënten met colorectaal carcinoom (CRC) hebben zelf een verhoogd risico op CRC. Dat wil zeggen dat hun risico tenminste twee maal zo hoog is als het bevolkingsrisico van 5-6%. Het is belangrijk dat deze mensen tijdig herkend worden, zodat ze zeer effectieve preventieve maatregelen kunnen nemen, waaronder regelmatige colonoscopieën (darmonderzoeken). Uit eerder onderzoek is echter gebleken dat slechts 12-30% van de mensen met een verhoogd familiair risico op CRC verwezen wordt voor erfelijkheidsonderzoek of preventieve colonoscopieën. Dit proefschrift bevat de resultaten van de RISCO-studie (risico op colorectaal carcinoom) en aanvullende onderzoeken die gedaan zijn om de identificatie en verwijzing van CRC-patiënten en hun familieleden met een verhoogd familiair risico te verbeteren.

Hoofdstuk 1 is een algemene introductie, met informatie over het familiair risico op CRC en de bijbehorende preventieve maatregelen. Volgens de huidige richtlijnen zijn dit: erfelijkheidsonderzoek bij een hoog familiair risico (meer dan 15%); preventieve colonoscopieën één keer in de 6 jaar vanaf 45-jarige leeftijd bij een matig verhoogd familiair risico (10-15%); en geen preventieve maatregelen anders dan deelname aan het bevolkingsonderzoek met fecaal occult bloedtesten (FOBT) bij een laag familiair risico op CRC (minder dan 10%), zodra dit bevolkingsonderzoek in Nederland start in 2013. Ook wordt beschreven waarom en hoe de studies in dit proefschrift tot stand zijn gekomen.

De eerste studies in het proefschrift betreffen onderzoeken naar de huidige identificatie en verwijzing van mensen met een verhoogd familiair risico op CRC in verschillende settings. Het eerste deel van **hoofdstuk 2** bevat een cross-sectionele studie waarin de huidige zorg voor CRC-patiënten is onderzocht in 18 Nederlandse ziekenhuizen. Er werd gekeken naar verwijzingen voor preventieve maatregelen vanwege een verhoogd familiair risico op CRC en de communicatie hierover, één jaar na de introductie van de nieuwe richtlijn. Hiervoor is gebruikt gemaakt van medisch dossieronderzoek en vragenlijsten onder CRC-patiënten en hun behandelend artsen (chirurgen en maag-darm-leverartsen). Dit onderzoek diende ook als de basismetingen voor de geclusterde gecontroleerde gerandomiseerde studie (c-RCT) beschreven in hoofdstuk 4 en 6.
Van de 437 patiënten die meededen, kon bij 358 (82%) het familiair risico op CRC worden bepaald. Van de 36 patiënten met een hoog familiair risico werd een derde (n=12) verwezen voor erfelijkheidsonderzoek. Familieleden van 21 van de 61 patiënten met een matig verhoogd familiair risico (34%) ondergingen preventieve colonoscopieën. In totaal werden 67% van de patiënten met een verhoogd familiair risico (n=65/97) en 23% van de patiënten met een laag familiair risico op CRC (n=61/261) verwezen voor preventieve maatregelen.

Betere verwijzing van CRC-patiënten en hun familieleden met een verhoogd familiair risico en het beperken van dergelijke verwijzingen voor mensen met een laag familiair risico op CRC zijn nodig voor betere en meer efficiënte preventie van kanker.

Kennis van artsen speelt een belangrijke rol bij het herkennen van mensen met een verhoogd familiair risico op CRC. Dit is onderzocht in het tweede deel van **hoofdstuk 2**. Maag-darm-leverartsen, chirurgen en klinisch genetici (in opleiding) in heel Nederland en huisartsen in de regio Nijmegen (n=2169) kregen een digitale vragenlijst toegestuurd. Deze bestond uit tien casus, waarin CRC-patiënten en hun familiegeschiedenis werden beschreven, met de vraag om voor iedere casus het familiair risico op CRC (hoog, matig of laag) en de passende preventieve maatregel (respectievelijk erfelijkheidsonderzoek, surveillance colonoscopieën, of geen van beide) te geven. Er deden 312 artsen mee (14%). Het familiair risico op CRC werd bij 55% van de casus goed ingeschat; bij 65% werd de juiste preventieve maatregel geadviseerd. Hieruit concluderen wij dat het verhogen van de kennis bij artsen nodig is en mogelijk leidt tot betere preventie van kanker.

In **hoofdstuk 3** is de prevalentie van een positieve familieanamnese en van een verhoogd familiair risico op CRC onderzocht in deelnemers aan een proefbevolkingsonderzoek naar CRC-screening. Bij 324 deelnemers met een positieve fecaal occult bloedtest (FOBT) werd de familieanamnese afgenomen door een ervaren arts of verpleegkundige. Zes procent van de deelnemers (n=17) had een verhoogd familiair risico op CRC. Als het familiair risico bepaald wordt in alle deelnemers met een positieve FOBT en deelnemers en hun familieleden met een verhoogd risico op CRC verwezen worden voor preventieve colonoscopieën en/of erfelijkheidsonderzoek, kunnen in Nederland jaarlijks 172-184 extra gevallen van CRC voorkómen worden.

De bevindingen uit de RISCO-studie en eerdere onderzoeken tonen aan dat veel mensen met een verhoogd familiair risico op CRC niet verwezen worden voor preventieve maatregelen. Dit leidt tot onnodige morbiditeit en mortaliteit. Er is dus nog veel ruimte voor verbetering. In het tweede deel van dit proefschrift worden de ontwikkeling en evaluatie van verbeterstrategieën beschreven. Het doel van deze strategieën is het verbeteren van de identificatie en verwijzing van deze mensen met een verhoogd familiair risico op CRC.

Hoofdstuk 4 bestaat uit een studieprotocol voor een geclusterde gerandomiseerde gecontroleerde studie (c-RCT). In negen van de in hoofdstuk 2 genoemde ziekenhuizen werd alleen de richtlijn erfelijke darmkanker verspreid (controlegroep). De andere negen ziekenhuizen (interventiegroep) kregen een veelzijdige implementatiestrategie aangeboden, bestaande uit een website voor CRC-patiënten en artsen, patiëntenfolders, en scholing en

verwijskaartjes voor artsen. In een effectevaluatie werd bepaald voor hoeveel patiënten het familiair risico op CRC goed werd berekend, geïnterpreteerd en gecommuniceerd, voor en na het invoeren van de implementatiestrategie. Het gebruik van de hulpmiddelen en de ervaring van CRC-patiënten en artsen met de hulpmiddelen werden gemeten in een procesevaluatie.

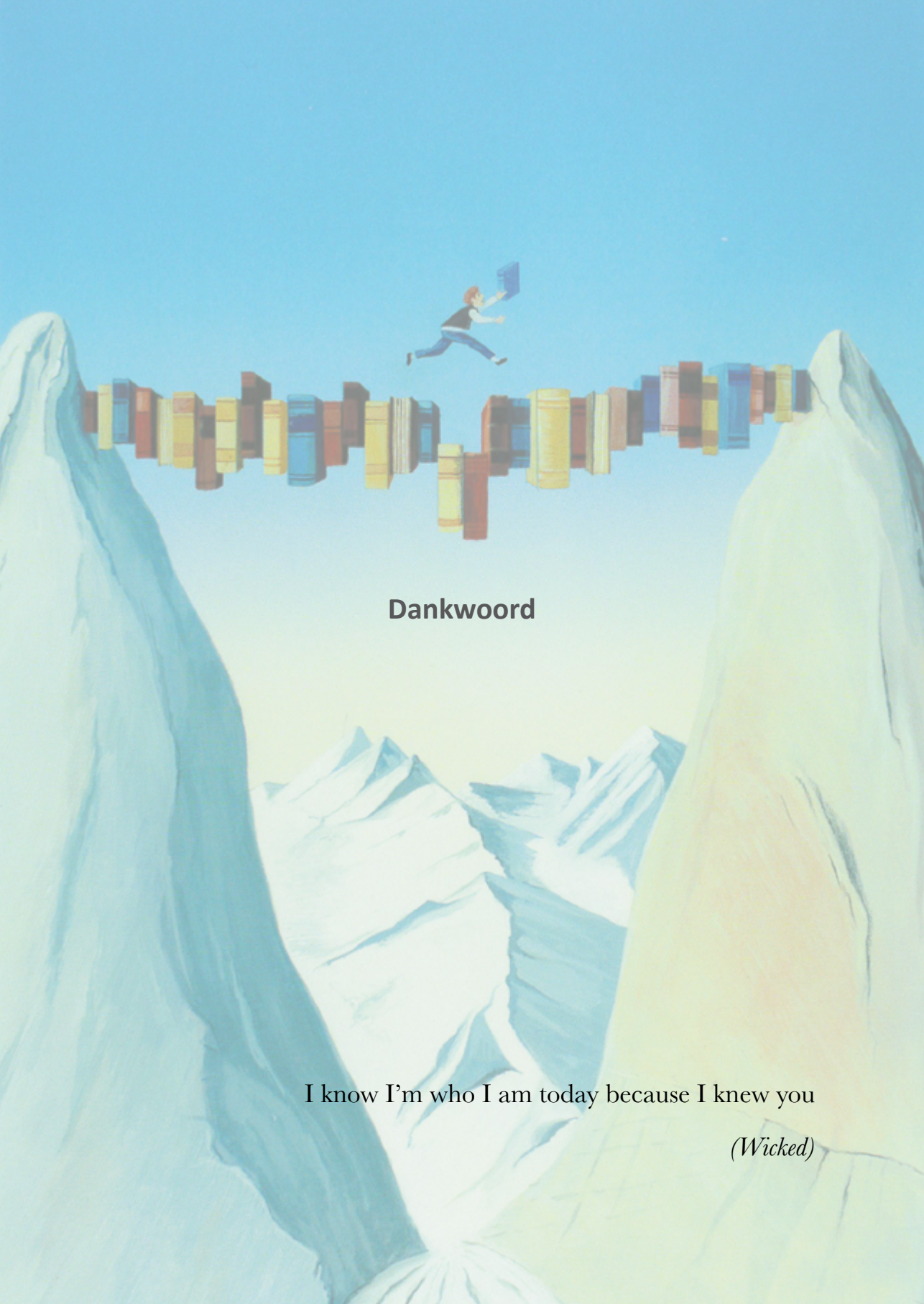
De ontwikkeling en het pilot-testen van de RISCO-website is beschreven in **hoofdstuk 5**. Deze website werd ontwikkeld door artsen, patiënten en wetenschappers. De website bevat evidence-based informatie over het familiair risico op CRC, rekenprogramma's waarmee artsen en patiënten dit risico kunnen berekenen, en een keuzehulp waarmee patiënten met een hoog familiair risico kunnen bepalen of zij verwezen willen worden voor erfelijkheidsonderzoek. Twintig CRC-patiënten en 12 artsen deden mee aan de pilotstudie van de website. Na het doorvoeren van verbetersuggesties van de eerste gebruikers, vooral in de navigatie en de keuzehulp, vonden patiënten en artsen de informatie goed te begrijpen en de website makkelijk te gebruiken en nuttig om te bepalen welke preventieve maatregelen geïndiceerd waren. Patiënten zagen de website vooral als bron van informatie, terwijl artsen de website vooral wilden gebruiken om te bepalen of hun patiënten in aanmerking kwamen voor preventieve maatregelen.

In **hoofdstuk 6** worden de resultaten van de geclusterde gerandomiseerde gecontroleerde studie (c-RCT) gepresenteerd. Bij 392 van de 476 patiënten (82%) in de nameting kon het familiair risico op CRC bepaald worden. Hun gegevens werden vergeleken met de 358 CRC-patiënten uit de voormeting (hoofdstuk 2). Van de patiënten met een hoog familiair risico werd 33% in de voormeting verwezen voor erfelijkheidsonderzoek (n=12/36); in de nameting was dit 15% (n=7/46, p=0.003) in zowel de interventiegroep als de controlegroep. Familieleden met een matig verhoogd familiair risico in de interventiegroep ondergingen minder vaak preventieve colonoscopieën (n=5/26, 19%) dan in de controlegroep (n=19/46, 41%; p=0.015) en de voormeting (interventiegroep 33%, n=13/39; controlegroep 36%, n=8/22; p>0.05 voor beide groepen).
Van de 140 patiënten in de interventiegroep gebruikte 67% de website (n=94) en lazen 34 patiënten (24%) de folder. Patiënten gaven de voorkeur aan advies van hun arts wanneer het ging om de keuze om verwezen te worden voor preventieve maatregelen terwijl de folders en website gewaardeerd werden als aanvullende hulpmiddelen. Van de 72 artsen gebruikte 35% de website (n=25) en nam tweederde deel aan de scholing (n=48). Artsen beoordeelden de scholing en de verwijskaartjes als meest nuttige hulpmiddelen. De lage verwijzingspercentages en beperkt gebruik van de hulpmiddelen suggereren dat aanvullende implementatiestrategieën nodig zijn.

Naast de hulpmiddelen die in de c-RCT zijn onderzocht, is ook een kortere digitale verwijstest ontwikkeld. In het in **hoofdstuk 7** beschreven onderzoek werd de sensitiviteit van de verwijstest gemeten voor het identificeren van patiënten met een hoog familiair risico op CRC. Hiervoor werden retrospectief stamboomgegevens van 420 mutatiedragers uit 81 families met het Lynchsyndroom in de verwijstest ingevoerd om te bepalen of verwijzing voor erfelijkheidsonderzoek werd geadviseerd. De sensitiviteit van de verwijstest was 91% voor mutatiedragers die zelf CRC hadden (n=164), en 73% voor alle mutatiedragers. De bruikbaarheid werd getest door te meten hoe goed niet-medisch personeel verwijsadvies kon geven met behulp van de verwijstest. Na een korte uitleg gaven de 20 deelnemers in 84% van zeven klinische casus het juiste verwijsadvies. Tenslotte beantwoordden 256/2470 gebruikers (10%) vier vragen over het nut van de verwijstest. Hiervan was 71% positief over de verwijstest, omdat deze meer duidelijkheid gaf over hun familiair risico op CRC en preventieve maatregelen en omdat de test ze geruststelde.

Adviezen voor preventieve maatregelen worden beter opgevolgd wanneer deze adviezen op maat gemaakt zijn en men overtuigd is van het nut ervan. In een in **hoofdstuk 8** beschreven studie werd onderzocht hoe erfelijkheidsadvies kan worden verbeterd. Mensen die werden verwezen voor erfelijkheidsonderzoek konden van een lijst met 45 items over de inhoud en vorm van erfelijkheidsadvisering aangeven hoe belangrijk zij deze items vonden. Deelnemers (n=48) vonden vooral informatie over het familiair risico op CRC (100%) en preventieve maatregelen (98%) zeer belangrijk, evenals sensitieve communicatie (100%). Meer aandacht voor deze onderwerpen kan mogelijk leiden tot meer tevredenheid over erfelijkheidsadvisering en het beter opvolgen van adviezen voor preventieve colonoscopieën.

In een algemene discussie in **hoofdstuk 9** gaan we in op bovenstaande bevindingen, de beperkingen van het onderzoek en de implicaties voor patiëntenzorg en toekomstige onderzoeken. Onze algemene conclusie is dat zelfs na de introductie van een veelzijdige implementatiestrategie minder dan de helft van de CRC-patiënten met een verhoogd familiair risico werd verwezen voor preventieve maatregelen volgens internationale richtlijnen, zoals erfelijkheidsonderzoek voor een hoog familiair risico en preventieve colonoscopieën voor een matig familiair risico. Daarom is het noodzakelijk dat er nieuwe strategieën worden ontwikkeld om het aantal verwijzingen voor preventieve maatregelen verder te verbeteren. We hebben aangetoond dat het zinvol kan zijn om hiervoor op artsen en andere zorgverleners in te zetten. Daarnaast adviseren wij dat patiënten meer actief deel gaan nemen aan hun eigen zorg. Gezamenlijke inzet van alle betrokkenen is nodig om een echte verbetering te bewerkstelligen van het gebruik van zeer effectieve maatregelen om kanker te voorkómen bij darmkankerpatiënten en hun familieleden met een verhoogd familiair risico.



Dankwoord

I know I'm who I am today because I knew you

(Wicked)

DANKWOORD

Nu mijn promotietraject (bijna) is afgerond, rest mij nog één ding: heel veel mensen te bedanken. Het waren mooie jaren, waarin ik veel heb geleerd en genoten. Zonder jullie was het me niet gelukt.

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Geachte leden van de RISCO-projectgroep en RISCO-stuurgroep, heel erg bedankt voor het bedenken van deze studie en jullie inspirerende commentaar. Geachte leden van de manuscriptcommissie en oppositiecommissie, bedankt voor het lezen en goedkeuren van mijn manuscript en jullie bijdrage aan deze bijzondere plechtigheid. Ook onze coauteurs wil ik hartelijk bedanken voor hun medewerking en commentaar. Ik heb er veel van geleerd.

Dear prof. Elwyn, dear Glyn: thank you for your part in the RISCO study. I wish you all the best in the USA and UK and please remember: there is no need to apologize for not providing comments on a paper within 48 hours.

Mijn kamergenoten, keldergenoten, kantoortuinmaatjes en alle andere collega's bij Genetica en IQ healthcare wil ik bedanken voor de gezelligheid, inspiratie, wijze lessen en steun in de afgelopen jaren. En niet te vergeten de borrels, film- en spelletjesavonden, zanglessen, tafeltennismatches, lunches, barbecues en andere etentjes, etcetera.

Inge: heerlijk dat wij de afgelopen 3½ jaar samen konden werken, al was het in de kelder. Heel veel succes met je onderzoek, je komt er wel.
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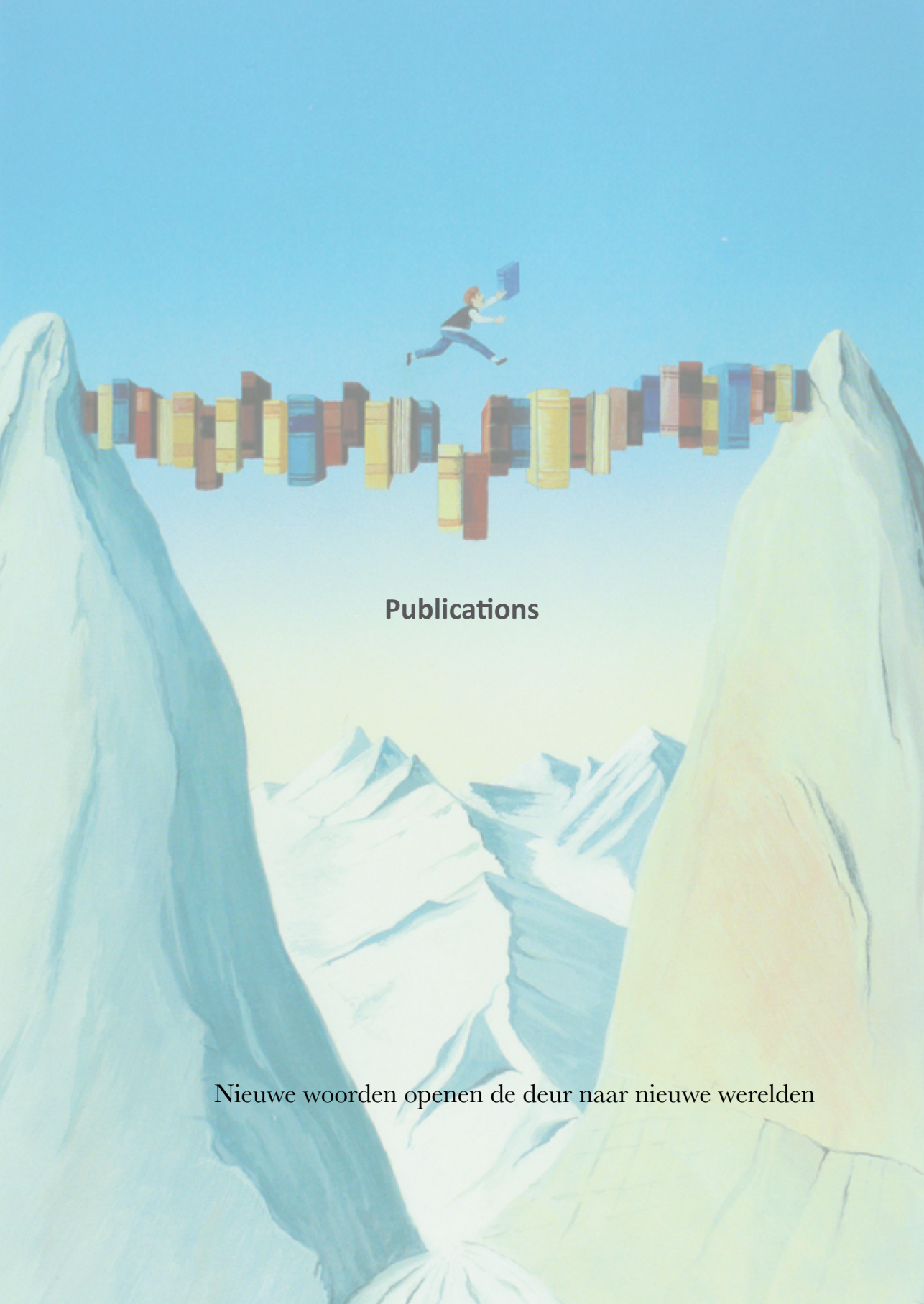


Publications

Nieuwe woorden openen de deur naar nieuwe werelden

PUBLICATIONS

N. Dekker, R. Hermens, F. Nagengast, W. van Zelst-Stams, N. Hoogerbrugge, RISCO study group. Familial colorectal cancer risk assessment in patients needs further improvement for more cancer prevention in relatives. Accepted for publication in Colorectal Disease, 2013.

S. Salemink, N. Dekker, C. Kets, E. van der Looij, W. van Zelst-Stams, N. Hoogerbrugge. Focusing on patient needs and preferences may improve genetic counseling for colorectal cancer. J Gen Couns 2013;22:118-124.

N. Dekker, L. van Rossum, M. Van Vugt-van Pinxteren, S. van Stiphout, R. Hermens, W. van Zelst-Stams, M. van Oijen, R. Laheij, J. Jansen, N. Hoogerbrugge. Adding familial risk assessment to FOBT can increase the effectiveness of population-based colorectal cancer screening. Eur J Cancer 2011;47:1571-1577.

N. Dekker, R. Hermens, G. Elwyn, T. van der Weijden, F. Nagengast, P. van Duijvendijk, S. Salemink, E. Adang, J. van Krieken, M. Ligtenberg, N. Hoogerbrugge. Improving calculation, interpretation and communication of familial colorectal cancer risk: Protocol for a randomized controlled trial. Impl Sci 2010,5:6.

N. Dekker, E. van Dorst, R. van der Luijt, M. van Gijn, M. van Tuil, J. Offerhaus, M. Ausems. Acceptance of genetic counseling and testing in a hospital-based series of patients with gynecological cancer. Accepted for publication in Journal of Genetic Counseling, 2012.

S. van den Broek, B. Muller, N. Dekker, A. Bootsma, O. ten Cate. Effect of the new Bologna bachelor degree on career considerations of medical students in one medical school. Med Teach 2010;32:997–1001.

N. Dekker, M. van Kempen, D. Lindhout, O. van Nieuwenhuizen, E. Brilstra. Epilepsie en het SCN1A-gen. Ned Tijdschr Kindergen 2008;5:254-258.

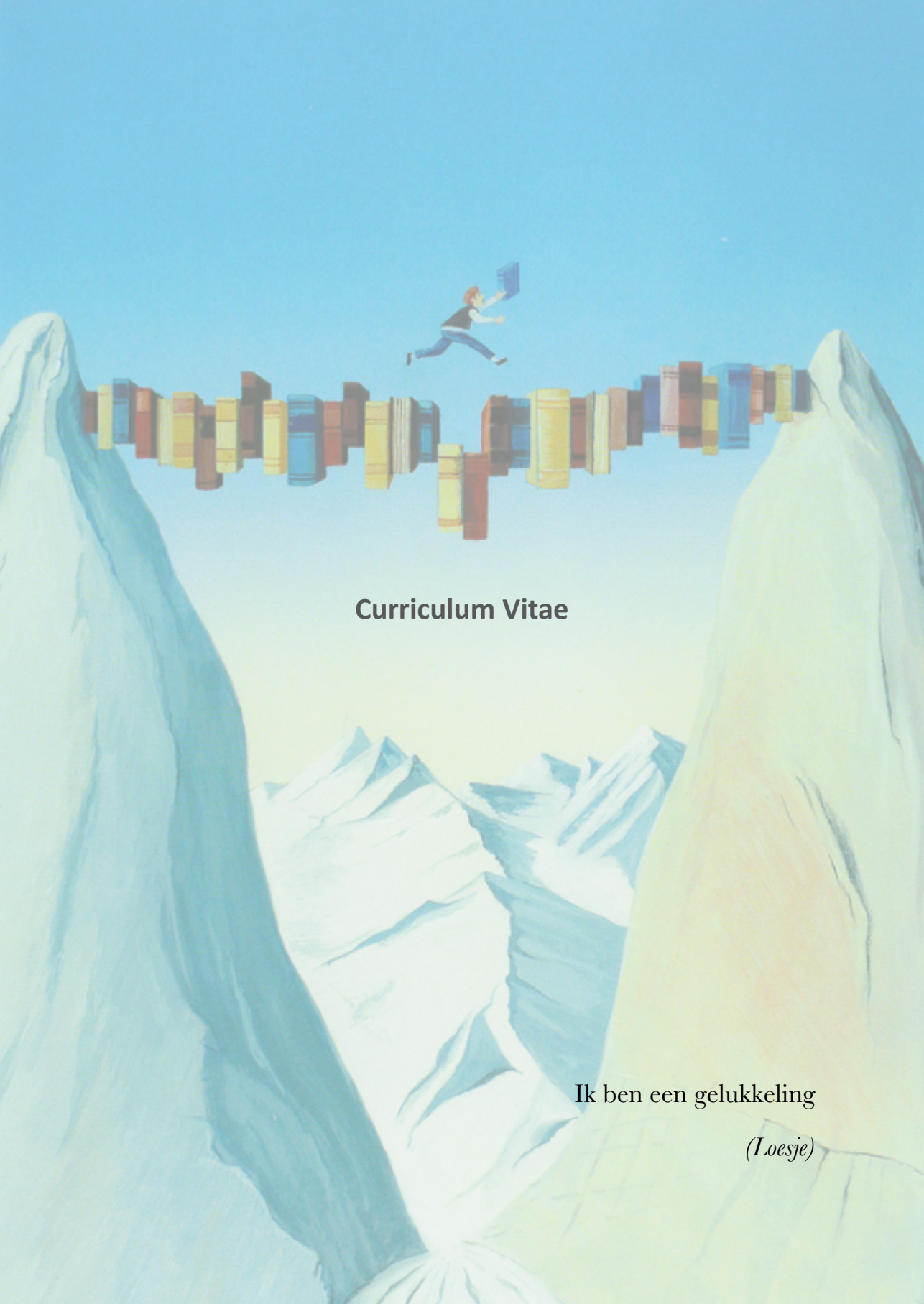
R. ten Brinke, N. Dekker, M. de Groot, D. Ikkersheim: Evidence Based Case Report: Lowering HbA1c in type 2 diabetics results in reduced risk of Coronary Heart Disease and all-cause mortality. Prim Care Diab 2008;2:45-49.

Submitted

N. Dekker, R. Hermens, G. Elwyn, J. de Wilt, F. Nagengast, J. van Krieken, M. Ligtenberg, T. van der Weijden, R. Sijmons, W. van Zelst-Stams, N. Hoogerbrugge, RISCO study group. Improving recognition and referral of patients with an increased familial risk of colorectal cancer: results from a randomised controlled trial.

N. Dekker, R. Hermens, A. Mensenkamp, M. Ligtenberg, W. van Zelst-Stams, N. Hoogerbrugge. Easy-to-use online referral test detects most patients with an increased familial colorectal cancer risk.

N. Dekker, R. Hermens, G. Elwyn, P. van Duijvendijk, F. Nagengast, W. van Zelst-Stams, N. Hoogerbrugge. Stepwise optimisation of web-based interventions for familial colorectal cancer: participation of patients and clinicians.



Curriculum Vitae

Ik ben een gelukkeling

(Loesje)

CURRICULUM VITAE

Nicky Dekker werd op 25 juni 1984 geboren in Amsterdam. In 2001 behaalde zij haar VWO-diploma aan het Colegio Arubano (Oranjestad, Aruba) als bestgeslaagde van haar jaar. Na haar eindexamen verhuisde zij naar Nederland om Geneeskunde te studeren aan de Universiteit Utrecht. Tijdens haar studie liep zij verschillende coschappen in het buitenland (Aruba en Zuid-Afrika). Tijdens een keuzecoschap en twee wetenschappelijke stages bij de afdeling Medische Genetica van het UMC Utrecht werd haar interesse voor de genetica in het algemeen en de oncogenetica in het bijzonder gewekt. Na het afronden van haar studie in 2008 ging zij als basisarts werken op de afdeling Klinische Genetica van het UMC St Radboud te Nijmegen. In 2009 startte zij daar haar promotieonderzoek op de afdelingen Klinische Genetica en IQ healthcare, wat leidde tot dit proefschrift. In 2012 verhuisde zij terug naar haar geboortestad, waar zij momenteel werkzaam is als postdoc op de afdeling Psychosociaal Onderzoek en Epidemiologie van het Antoni van Leeuwenhoek. Zij coördineert hier een nationaal project waarin nazorg opgezet wordt voor overlevenden van (non-)Hodgkinlymfoom.


RIS CO
Familierisico op Darmkanker